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August 1946

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The American Journal of Medicine

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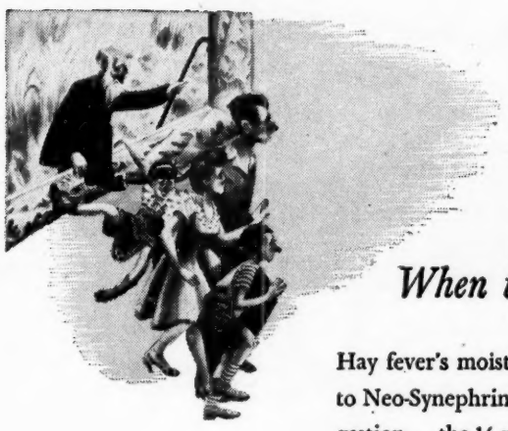

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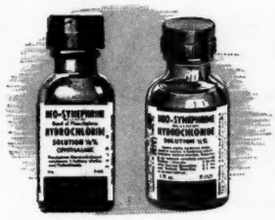

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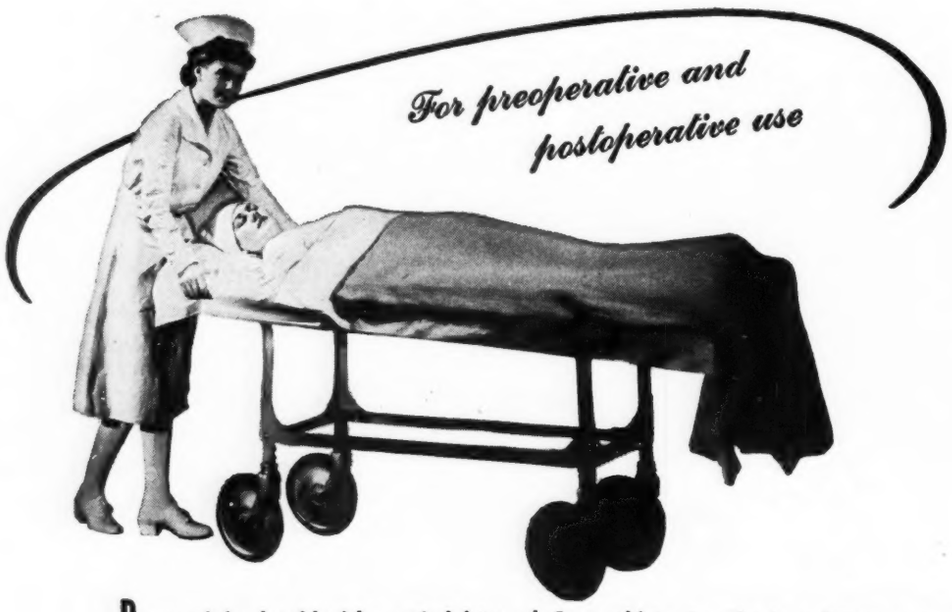

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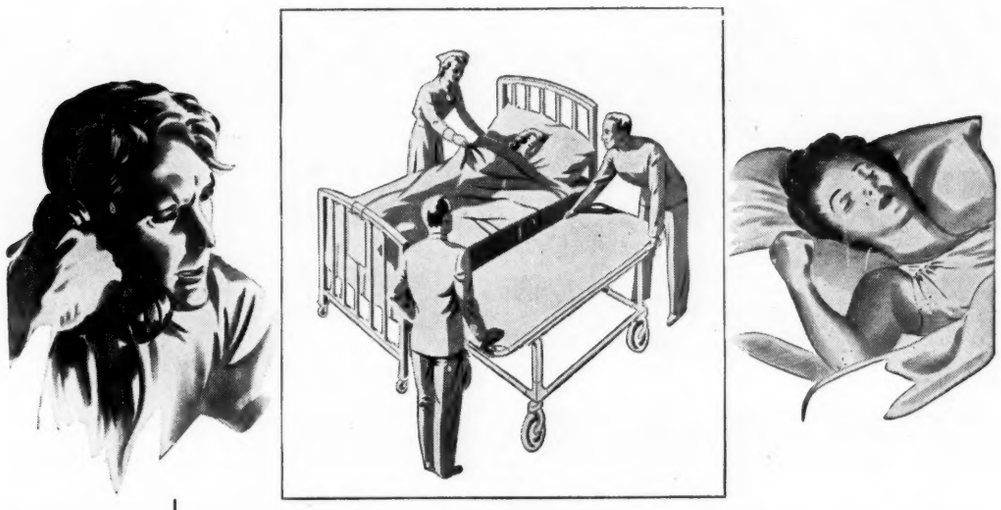

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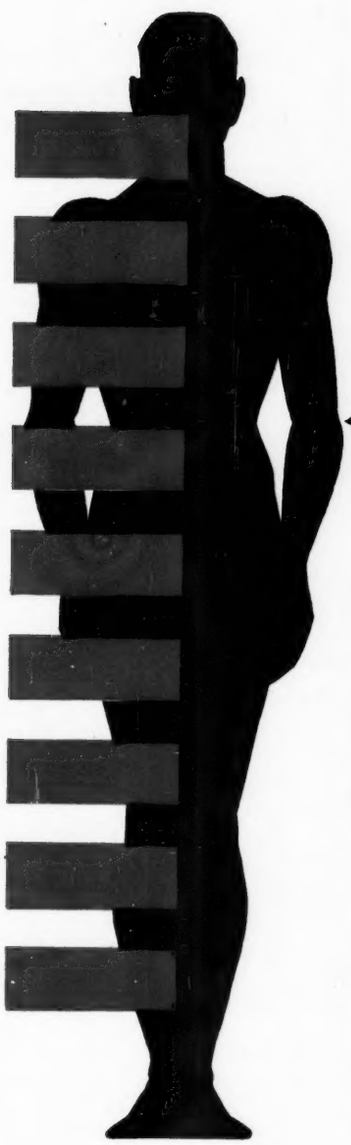

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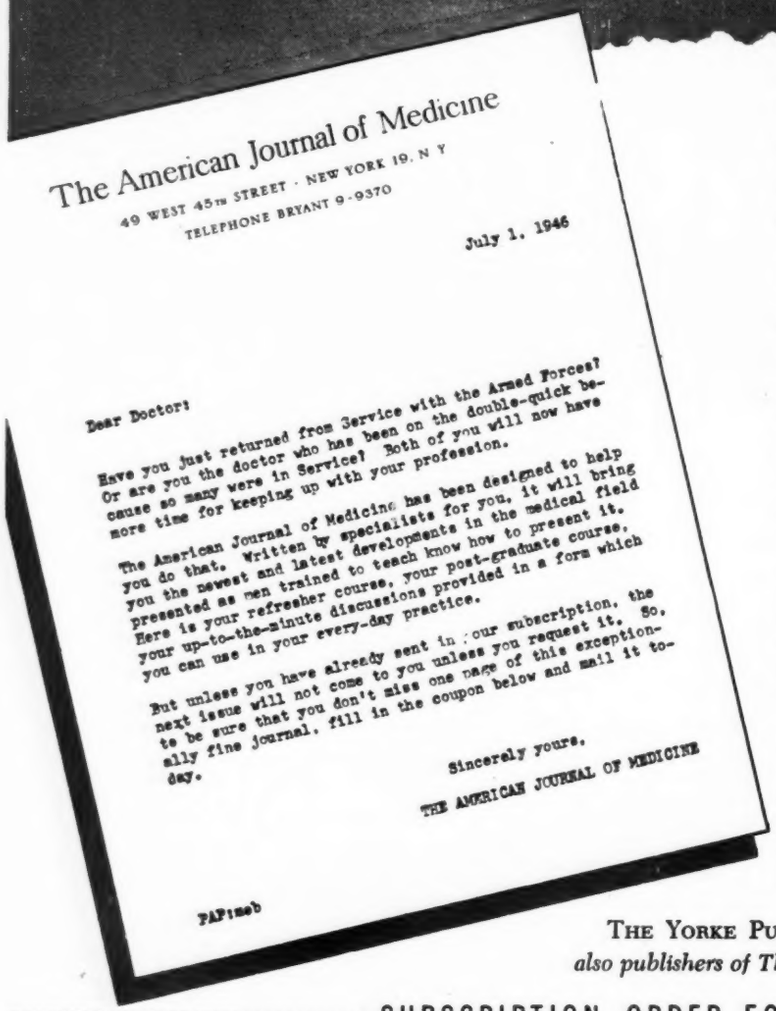

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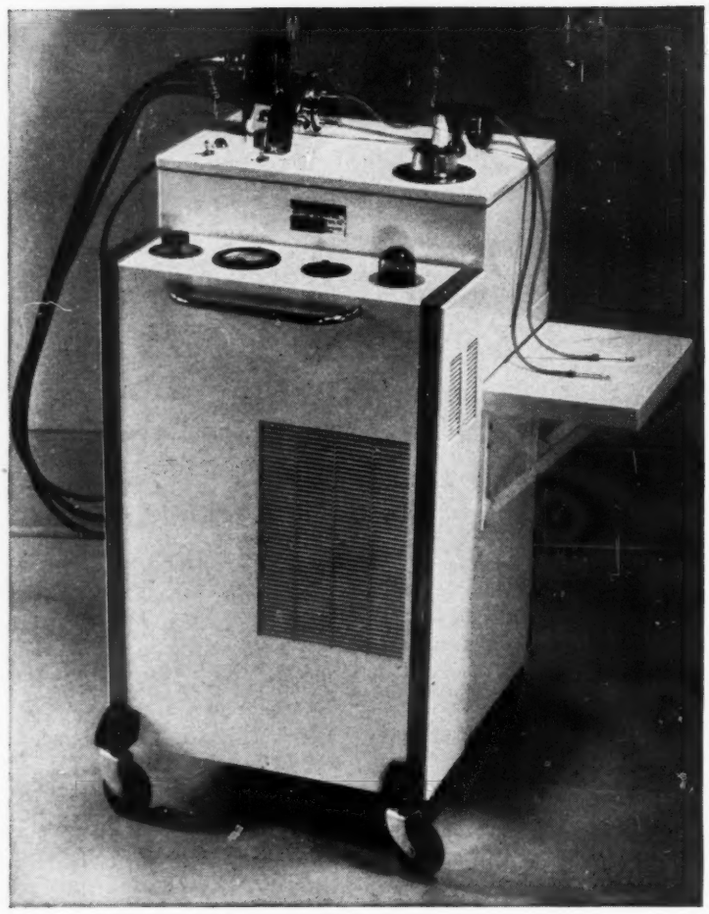

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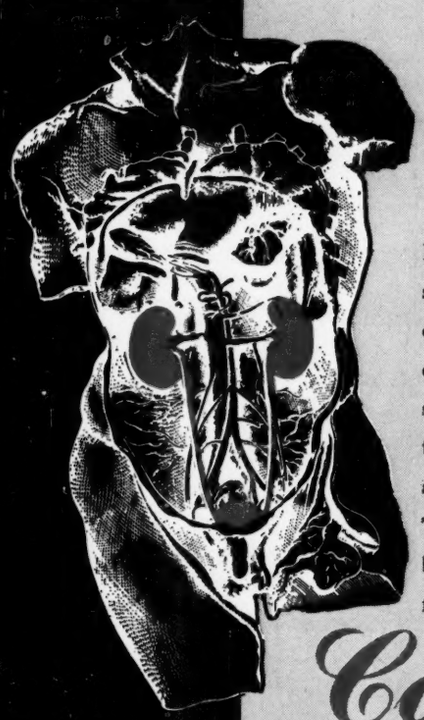

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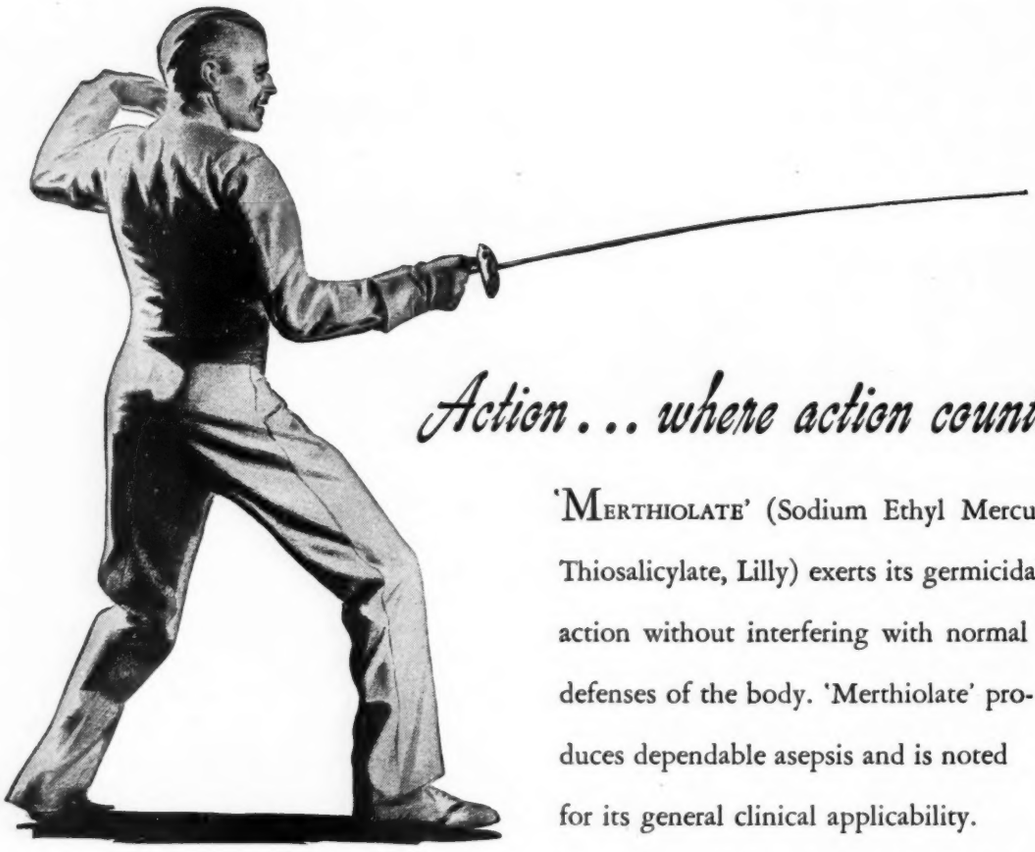

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Metabolic Changes Induced by Synthetic 11-Dehydrocorticosterone Acetate*

Including Comparative Studies with Synthetic Desoxycorticosterone Acetate, Natural 17-Hydroxycorticosterone and Lipo-Adrenal Cortex (Preliminary Report)

PETER H. FORSHAM, M.D., GEORGE W. THORN, M.D., GRACE E. BERGNER, M.D.†

and KENDALL EMERSON, JR., M.D.

BOSTON, MASSACHUSETTS

To date 11-desoxycorticosterone is the only synthetic adrenal cortical hormone preparaton available for clinical use. It is generally recognized that while 11-desoxycorticosterone therapy restores electrolyte balance, plasma volume and blood pressure to normal in patients with Addison's disease, it does not correct the fundamental disturbance in carbohydrate metabolism, restore muscle function to normal or reduce pigmentation significantly.[1] Studies with whole adrenal cortical extracts and with naturally occurring adrenal steroids suggest that compounds with an oxygen atom at the carbon-11 position possess "carbohydrate-regulating" capacity; furthermore, the addition of an oxygen atom at the carbon-17 position enhances this particular property.[2] The sodium and chloride-retaining capacity of both of these groups of compounds, however, is definitely less than that of 11-desoxycorticosterone.[3] Experimental studies indicate that treatment with corticosterone, dehydrocorticosterone or 17-hydroxycorticosterone is adequate for maintenance of bilaterally adrenalectomized animals.[2] It has not been possible to test the efficacy of these compounds in maintaining

* From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Mass. This study was aided in part by a grant from the Committee on Research in Endocrinology, National Research Council.

† Commonwealth Fund Fellow.

patients with Addison's disease because of the unavailability of naturally occurring crystalline adrenal steriods. The recent syntheses announced by Reichstein[4] and by Kendall[5]* permit the large scale preparation of adrenal steroid compounds with an oxygen atom at the carbon-11 position. The present report is concerned with our clinical experience in the use of 11-dehydrocorticosterone (Compound A, Kendall) in the treatment of Addison's disease. The dehydrocorticosterone acetate used in these studies was synthesized by Merck and Co. according to the method of Kendall.

The synthesis of desoxycorticosterone acetate provided an unlimited quantity of adrenal hormone at a cost which most patients could afford. The use of pellets (125 mg. tablets) of crystalline material implanted subcutaneously once a year has been found to be a convenient and very satisfactory method of administering the hormone. A limiting factor in desoxycorticosterone acetate therapy, however, is the inability of this preparation to prevent bouts of hypoglycemia particularly in patients with intercurrent infections or gastrointestinal upsets. During such crises it has been necessary to provide glucose intravenously and, as an added protection, whole adrenal extract therapy at frequent intervals.[6]

Patients with Addison's disease may be maintained in excellent condition with large doses of aqueous adrenal cortical extract given subcutaneously two or three times daily.[7] As far as can be ascertained such therapy affords complete replacement. The necessity for frequent injections and the relatively high cost of this form of therapy ($7.00 to $10.00 daily) are limiting factors in its clinical use; another factor which has not been appreciated fully is the relatively limited quantity of naturally occurring extract which is or can be made available. On several occasions during the past years we have been unable to obtain commercial extract for patients in crisis. Unfortunately, another disadvantage in using aqueous adrenal cortical extracts in the treatment of disturbances in carbohydrate metabolism in patients with Addison's disease is the fact that none of these commercial aqueous extracts is assayed with respect to this particular factor. Extracts from different manufacturers may vary greatly in potency, and different batches of extract from the same manufacturer may also vary considerably from time to time in respect to "carbohydrate-regulating" capacity. Considerable confusion exists, therefore, in regard to the efficacy and exact dosage of these preparations in emergency situations.

Fortunately, in the past two years there has been made available a purified preparation of adrenal steroids derived from hog adrenals and standardized against crystalline corticosterone and 11-dehydro-17-hydroxycorticosterone for its "carbohydrate-regulating" potency.* This preparation has been found to be effective in the treatment of hypoglycemic crises and in improving muscle function.[8] Since this preparation is absorbed slowly as an oil solution, intramuscular injections once or twice daily have been adequate in most instances. Again, however, the high cost of preparation and limited supply restrict its use. In our experience it has usually been necessary to provide a diet high in sodium chloride or to give supplementary desoxycorticosterone acetate when Lipo-Adrenal Cortex is used in the treatment of the more severe cases of Addison's disease, because this purified preparation induces only moderate sodium and chloride retention.

* The method for introduction of oxygen at carbon 11 and preparation of dehydrocorticosterone was given at a meeting held March 11th in Atlantic City. At this time reports on the physiologic activity of the synthetic material provided ample proof that the natural and synthetic hormones produced physiologic responses which were identical.

* Upjohn's Lipo-Adrenal Cortex.

From these studies on the purified natural extract, one might suspect that a single synthetic preparation, high in "carbohydrate-regulating" potency, might require supplementation with a steroid compound of high-sodium and chloride retaining capacity, or at least a diet very high in sodium chloride content, for the most effective therapeutic results.

In 1940, Thorn, Koepf, Lewis and Olsen[9] reported the metabolic changes which followed the administration of a single large dose (85 mg.) of corticosterone in a patient with Addison's disease. The crystalline hormone was prepared from beef adrenals by Kendall. Following the administration of this large dose of corticosterone there occurred (1) a small increase in fasting blood sugar, (2) a decrease in fasting respiratory quotient, (3) an increase in basal metabolic rate, (4) a more diabetic-like type of glucose curve following intravenous administration of glucose, and (5) amelioration of usual symptoms of hypoglycemia at the end of the intravenous glucose tolerance test. In this respect 33 mg. of 17-hydroxy-11-dehydrocorticosterone or 50 cc. of adrenal cortex extract was somewhat more effective than 85 mg. of corticosterone. The limited supply of natural crystalline steroids precluded more than a single experiment. It was also obvious from these experiments that 50 cc. of extract which contained a total of only 10 mg. of identified crystalline steroids was more active than identical amounts of either 17-hydroxy-11-dehydrocorticosterone or corticosterone.

In the present study we have measured the effect of dehydrocorticosterone acetate in oil on the renal excretion of electrolytes and nitrogen in patients with Addison's disease; we have investigated the "carbohydrate-regulating" potency of this preparation and have also studied its effectiveness as maintenance therapy; we have made comparative studies with natural crystalline 17-hydroxycorticosterone* as well as with a purified adrenal cortical extract (Upjohn's Lipo-Adrenal Cortex†). The effect of administration of synthetic Compound A has also been studied in a normal human subject.

METHODS

Studies on patients with classical signs and symptoms of Addison's disease form the basis of this report. (Table 1.) The severity of the adrenal cortical deficiency in these patients is indicated by the very low urinary 17-ketosteroid values, i.e., for the six female patients the average value is 0.9 mg. per twenty-four hours (range 0 to 2.6); for the eight male patients the average value is 3.1 mg. per twenty-four hours (range 2.0 to 4.4).

TABLE 1
ADDISON'S DISEASE

Patient	Age	Sex	Duration of Disease	Etiology	17-Ketosteroid Excretion mg./24 Hr.*
J. C. . .	49	♂	13 years	T.B.	2.8
W. C. .	32	♂	13 years	Non-T.B.	3.6
J. P. . .	27	♂	10 years	T.B.	2.0
E. V. .	48	♂	9 years	? T.B.	2.0
H. J. . .	55	♂	8 years	T.B.	3.8
S. B. . .	26	♂	7 years	Non-T.B.	
N. M. .	43	♂	6 years	Non-T.B.	4.4
R. G. .	32	♀	6 years	Non-T.B.	2.6
M. N. .	45	♀	4 years	Non-T.B.	0
M. T. .	20	♀	4 years	Non-T.B.	0.2
M. F. .	48	♀	3 years	Non-T.B.	1.3
K. K. .	29	♂	2 years	Non-T.B.	3.2
E. H. .	42	♀	1 year	Non-T.B.	0.6
V. A. .	37	♀	9 months	Non-T.B.	2.8

* Normal average values: Males = 13.8 mg. daily. Females = 9.0 mg. daily.

Patients were studied on the Metabolism Ward of the Peter Bent Brigham Hospital. During the experimental periods they were maintained on a diet of constant liquid, sodium chloride, nitrogen and caloric in-

* The natural crystalline 17-hydroxycorticosterone used in these studies was provided through the kindness of Dr. M. H. Kuizenga of the Upjohn Company.

†This preparation was made available through the courtesy of Dr. E. G. Upjohn of the Upjohn Company.

take. The sodium content of the diet approximated 2 Gm. (5 Gm. sodium chloride equivalent). In addition 2 Gm. of sodium chloride was provided daily in a salt shaker. The diets were made up in a proportion of 5.0 Gm. of carbohydrate, 1.3 Gm. of protein, and 1.5 Gm. of fat per kilogram of body weight per day. When this yielded excessive calories, the total intake was reduced, but the proportion was maintained. This diet has been shown to yield a fasting (overnight) respiratory quotient of approximately 0.85 in normal adults. Food values were calculated from standard tables. The experimental periods ranged from three to five days, and the patients were maintained on the constant diet for several days prior to study. They were weighed daily, and blood pressure was taken in the basal state. Twenty-four-hour urine specimens were collected from 7:00 A.M. to 7:00 A.M., and daily aliquots were stored under toluol in a refrigerator. Special specimens for the determination of sodium, potassium and other electrolytes were stored in pyrex containers. Stools were checked as to number and consistency. In a few instances three-day specimens were homogenized, dried and then analyzed for nitrogen,[10] fat and fatty acids.[11] Venous blood specimens were drawn with a minimal stasis after a twelve-hour fast with the patient in basal condition. Certain of the samples such as those for chloride and carbon-dioxide combining power were drawn under oil, and all were processed within an hour, particular care being taken to separate serum and cells whenever estimations were carried out on separate blood constituents. Hematocrit (packed red cell volume) was estimated by the method of Wintrobe.[12] Total white blood count and differentiation of cells were performed during each of the experimental periods. Urine chloride was estimated by the mercuric nitrate titration method of Schales;[13] serum chloride by the method of Sendroy;[14] sodium in serum and urine by the method of Consolazio and Dill;[15] potassium by the method of Consolazio and Talbott;[16] carbon dioxide combining power by the Van Slyke manometric technic;[17] inorganic serum phosphorus by the method of Fiske and Subbarow;[18] inorganic and total phosphorus in the urine by the method of Allen;[19] total nitrogen and non-protein nitrogen by a modification of Daly's method;[20] total protein, serum albumin, and globulin by the method of Howe,[21] the protein being calculated by multiplying the total nitrogen value by 6.25. Urea nitrogen and urea and ammonia nitrogen were determined by the hypobromite method of Van Slyke[22] and served as a check on the total nitrogen, revealing also changes in the ratio of total to urea ammonia nitrogen. Uric acid was estimated by Archibald's* modification of the method of Kern and Stransky both in serum and urine;[23] blood urea nitrogen by a recent method of Archibald[24] and amino acids in the plasma and urine by the ninhydrin carbon dioxide method of Van Slyke and Hamilton and Van Slyke, MacFadyen, and Hamilton.[25,26] Creatinine determinations were run on the urine pools as a check on the accuracy of the collections, using the method of Folin and Wu,[27] and creatine was determined by the method of Lambert whenever measurable amounts were present.[28] Urea clearances expressed in terms of the percentage of normal were computed from appropriate tables in Peters' and Van Slyke's "Quantitative Clinical Chemistry."[29] These measurements were carried out with each period so as to control the renal factor in the varying nitrogen excretion.

Fasting blood sugar values were obtained on fluoride protected blood samples by the method of Folin and Malmros.[30] Pyruvic acid drawn into 30 per cent iodo-acetate

* We are indebted to Dr. R. M. Archibald who provided us with this method prior to publication.

according to Bueding[31] was estimated by the method of Friedemann and Haugen.[32] Cholesterol, both free and esterified, was determined by a modification of the method of Schoenheimer and Sperry.[33] An icteric index was taken on all patients as was a modified thymol turbidity test.[34] Bromsulfalein test was performed when indicated.

Intravenous glucose tolerance tests were run by a standard method[9] using venous blood. Respiratory quotients and basal metabolic determinations were estimated by routine methods. Tests for muscle function were carried out by placing a stimulating electrode on the ulnar nerve.* Condenser dosages of 1 millisecond duration were delivered at voltages giving maximal contraction of the ulnar muscle group. Stimulation frequency of one per second, two per second, four per second, and eight per second were used, each for a period of ninety seconds. Recovery was followed by recording the response to stimulation given every ten seconds. Frequency of stimulation at which fatigue occurred and the amount of posttetanic potentiation were measured.

Synthetic dehydrocorticosterone acetate (Merck) was administered intramuscularly, i.e., 5 mg. in 1 cc. of sesame oil with 10 per cent benzyl alcohol added as a preservative. Desoxycorticosterone acetate was injected intramuscularly as Percorten (Ciba) 5 mg. per cc. in sesame oil or administered in pellets of 125 mg. each, implanted subcutaneously in the infrascapular region.† The pellets are known to dissolve at a rate of approximately 0.5 mg. per day. Upjohn's Lipo-Adrenal Cortex (1 cc. being equivalent to 2 mg. of 11-dehydro-17-hydroxycorticosterone or 4 mg. of corticosterone) was also injected intramuscularly. This preparation is standardized biologically. Eschatin (Parke, Davis), purified aqueous extract containing no less than 50 dog units of adrenal cortical hormone per milliliter, was administered intravenously or subcutaneously.

OBSERVATIONS

CLINICAL CONSIDERATIONS

Preliminary experiments indicated that the sodium and chloride retaining effect of dehydrocorticosterone acetate in a daily dose of 10 to 30 mg. was inadequate for optimum maintenance in several of the patients with severe Addison's disease on a constant diet of moderate but restricted sodium chloride intake. For this reason metabolic studies on the effect of Compound A were made both with and without a supplementary dose of desoxycorticosterone acetate (1 to 2.5 mg. daily). In most instances the basic supplement of desoxycorticosterone acetate was instituted well in advance of the administration of Compound A.

During the control experimental period on the constant diet most of the patients lost weight slowly, the average being a loss of 0.1 to 0.2 kg. daily. During the period on Compound A therapy body weigh was maintained. With Compound A therapy alone no striking evidence of general clinical improvement was observed during the short periods of treatment (three to five days) except in the case of one patient V. A. (See Appendix.) The addition of Compound A therapy to a basic regimen of desoxycorticosterone acetate resulted in an improvement over and above that seen with desoxycorticosterone acetate a'one. This was characterized by an improved sense of well being, increased resistance to fatigue on prolonged moderate exertion, the elimination of postprandial weakness and occasional episodes of spontaneous hypoglycemia following overnight fasting. Furthermore, minor operations such as multiple tooth

* Dr. R. L. Swank devised the technic used in the evaluation of neuromuscular function, and the tests were carried out under his supervision.

† We are indebted to Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., for the Percorten solution and pellets.

extractions were well tolerated by three patients during Compound A therapy.

No local or general untoward reactions were observed in the fourteen patients treated with 10 to 60 mg. of synthetic dehydrocorticosterone acetate daily. During the short course of therapy no evidence of excessive sodium chloride retention or hypertension was observed in any of the patients with doses as large as 60 mg. daily. No local or generalized sensitivity to the solvent, sesame oil, was encountered.

RENAL EXCRETION OF ELECTROLYTES AND NITROGEN

Effect of 11-*Dehydrocorticosterone Acetate* 10 *to* 15 *mg. Daily.* In four experiments on three patients (J. C., N. M., and M. N.) given 10 to 15 mg. of Compound A daily there occurred an average daily increase in retention as compared to the control period of 14 m.eq. of sodium (range 11 to 23) and 21 m.eq. of chloride (range 7 to 31). [Table II, Fig. 1.] Potassium excretion was increased in two out of four experiments, the average increase for the entire group being 5 m.eq. per day. Increased nitrogen excretion was noted in three instances, the average for the four experiments being 0.5 Gm. of total nitrogen per day. Inorganic phosphorus excretion was increased in only one patient J. C. (Table II.)

Effect of 11-*Dehydrocorticosterone Acetate* 20 *to* 60 *mg. Daily.* Nine patients (ten experiments) were treated with 20 to 60 mg. of Compound A daily. (Table II.) In four experiments it was feasible to compare directly a control period without treatment of any type with one in which 30 to 60 mg. of Compound A was given daily (K. K., N. M., and M. T.). [Table II, Fig. 1.] The observations made on a typical case (M. T.) are summarized in Figure 2.

In six patients Compound A therapy was added to a basic regimen of desoxycorticosterone acetate. In order to obtain constant conditions for studying the effect of Compound A, the desoxycorticosterone ace-

TABLE II

CHANGES IN RENAL EXCRETION FOLLOWING 11-DEHYDROCORTICOSTERONE ACETATE THERAPY IN PATIENTS WITH ADDISON'S DISEASE*

Patient	Rx Daily Mg.	Sodium m.eq. per Day	Chloride m.eq. per Day	Potassium m.eq. per Day	Nitrogen Gm. per Day	Inorganic Phosphorus m.M. per Day	Duration of Treatment, Days
J. C.	10	−23	−28	+28	+2.3	+12.0	5
N. M.	10	−11	−31	−12	+0.4	− 1.5	5
N. M.	10	−11	−17	+16	−1.0	− 2.1	5
M. N.†	15	−11	− 7	−13	+0.1	0	5
J. C.†	20	−34	−30	+ 9	+1.7	+ 1.0	5
E. H.†	20	+ 2	−16	+ 1	+2.4	+ 6.0	3
E. V.†	20	−16	−33	+20	+2.8	+13.0	5
N. M.	30	−27	−30	+25	+1.4	+ 3.9	5
M. N.†	30	−29	−17	+ 9	+2.0	+ 6.0	3
J. P.†	30	− 7	− 3	− 4	−0.2	− 6.0	3
M. T.	30	−20	−26	+10	+1.5	+ 8.9	3
K. K.	30	−27	−39	+ 6	+1.4	+ 4.6	3
H. J.†	30	−14	− 8	+ 7	+1.0	0	2
K. K.	60	− 8	−20	+17	+1.1	+ 2.0	3

* All patients were maintained on a constant intake throughout this study.

† These patients were maintained on small doses of desoxycorticosterone acetate (1–2.5 mg. daily) throughout the entire experiment.

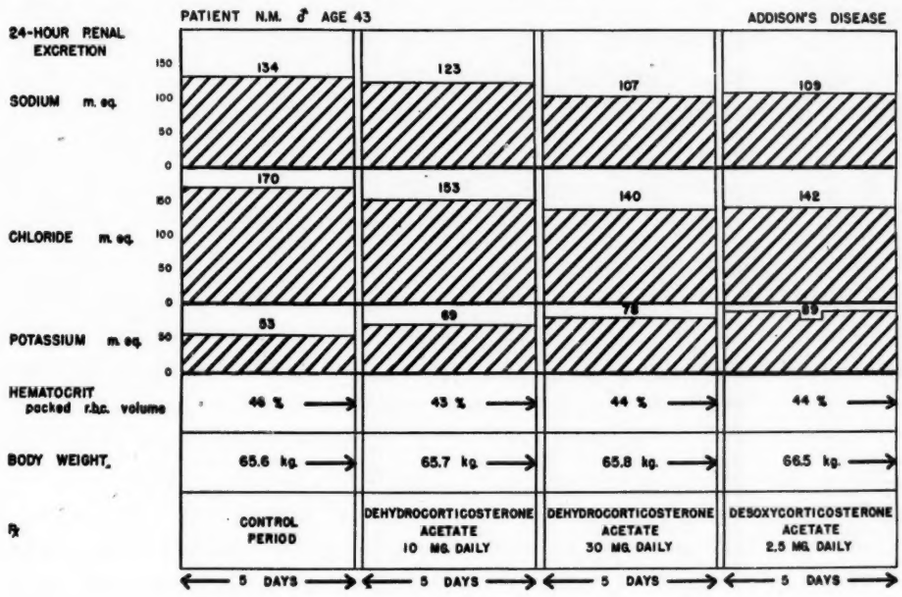
EFFECT OF ADRENAL STEROID THERAPY
ON RENAL EXCRETION OF ELECTROLYTES
PATIENT N.M. ♂ AGE 43
ADDISON'S DISEASE
24-HOUR RENAL EXCRETION
SODIUM m. eq.
150
100
50
0
134
123
107
109
CHLORIDE m. eq.
250
100
50
0
170
153
140
142
POTASSIUM m. eq.
50
0
83
69
78
85
HEMATOCRIT packed r.b.c. volume
46 %
43 %
44 %
44 %
BODY WEIGHT
65.6 kg.
65.7 kg.
65.8 kg.
66.5 kg.
℞
CONTROL PERIOD
DEHYDROCORTICOSTERONE ACETATE 10 MG. DAILY
DEHYDROCORTICOSTERONE ACETATE 30 MG. DAILY
DESOXYCORTICOSTERONE ACETATE 2.5 MG. DAILY
5 DAYS
5 DAYS
5 DAYS
5 DAYS

FIG. 1

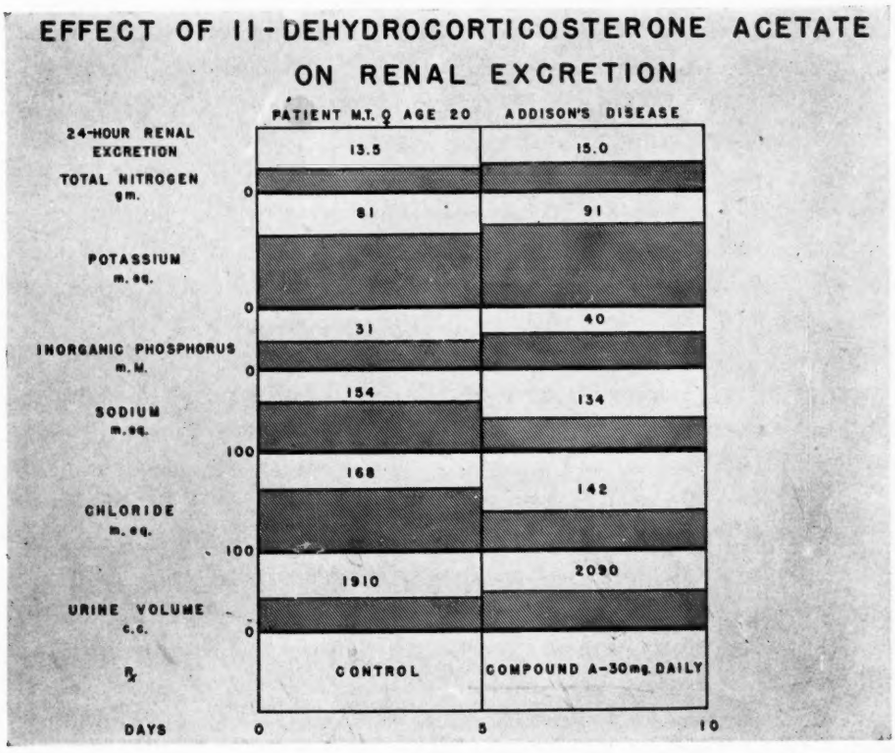
EFFECT OF 11-DEHYDROCORTICOSTERONE ACETATE
ON RENAL EXCRETION
PATIENT M.T. ♀ AGE 20
ADDISON'S DISEASE
24-HOUR RENAL EXCRETION
TOTAL NITROGEN gm.
13.5
15.0
0
POTASSIUM m. eq.
81
91
0
INORGANIC PHOSPHORUS m. M.
31
40
0
SODIUM m. eq.
154
134
100
CHLORIDE m. eq.
168
142
100
URINE VOLUME c.c.
1910
2090
0
℞
CONTROL
COMPOUND A-30mg. DAILY
DAYS
0
5
10

FIG. 2

tate was given in a constant dosage for a prolonged period prior to the administration of Compound A.

Sodium excretion was decreased in eight of nine patients during the period of Compound A therapy. (Table II.) The average decrease amounted to 18 m.eq. daily. (Table III.) Retention of sodium tended to be greater with the larger doses of hormone except for the case of K. K. when 60 mg. was used. *Chloride* excretion was decreased in all ten experiments on Compound A, the average decrease amounting to 23 m.eq. daily. *Potassium* excretion increased in nine of the ten experiments. The average increase amounted to 9 m.eq. for the entire group. *Inorganic phosphorus* excretion rose in eight of ten experiments, the average increase amounting to 4 m.M. daily. (Table III.)

TABLE III
SUMMARY OF CHANGES IN RENAL EXCRETION FOLLOWING COMPOUND A THERAPY

	Control Period	Compound A* Therapy
Sodium m.eq./24 hr.	119	101
Chloride m.eq./24 hr.	139	116
Potassium m.eq./24 hr.	77	86
Inorganic phosphorus m.M./24 hr	25	29
Total nitrogen gm./24 hr. . . .	9	10.2

* Average value for 14 experiments; average dose of Compound A—26 mg. (range 10–60).

An increase in *total nitrogen* excretion was observed in all but one case (J. P., Table II), the average daily increase for the group amounting to 1.2 Gm. daily. (Table III.) It occurred also in four additional experiments incomplete in some respects and hence not reported in Table II. The average increase in total nitrogen excretion in these four experiments was 1.3 Gm. daily. The dose of Compound A used in these latter experiments was 10 mg. daily in one patient and 30 mg. daily in three.

Since there was no significant change in urea clearance on Compound A as compared to the control period, improvement in renal function cannot be held responsible for the increased nitrogen excretion. The percentage of total nitrogen contributed by urea and ammonia combined remained essentially the same under Compound A treatment. It was found to be 87 per cent before (range 82 to 97 per cent) and 84 per cent (range 74 to 95 per cent) during therapy, there being a slight tendency toward a decrease in the majority of cases suggesting an increase in other nitrogen fractions.

A consistent increase in *uric acid* excretion occurred in all but one patient. (Fig. 3.) The average increase amounted to 140 mg., representing a 32 per cent increase over the control value in contrast to an 11 per cent increase in total nitrogen excretion. No significant change in serum uric acid was noted.

The daily urinary output of *alpha amino nitrogen* serving as a measure of the excretion of free amino acids also showed a significant increase in the single case in which it was studied (K. K.). During a period on 30 mg. of Compound A daily alpha amino nitrogen increased from the level of 107 mg. per day to a level of 176 mg. per day. This represented a 65 per cent increase in alpha amino nitrogen as compared to the 15 per cent increase observed in total nitrogen. During a period of 60 mg. of Compound A alpha amino nitrogen increased from a level of 90 mg. daily during the control period to a level of 160 mg. daily during the period on treatment. This represented a 78 per cent increase in alpha amino nitrogen as compared to an 11 per cent increase in total nitrogen excretion during this same period.

Creatinine excretion remained constant in the males under Compound A therapy. There was no creatinuria. However, four female patients showed creatinuria before Compound A treatment, the average value

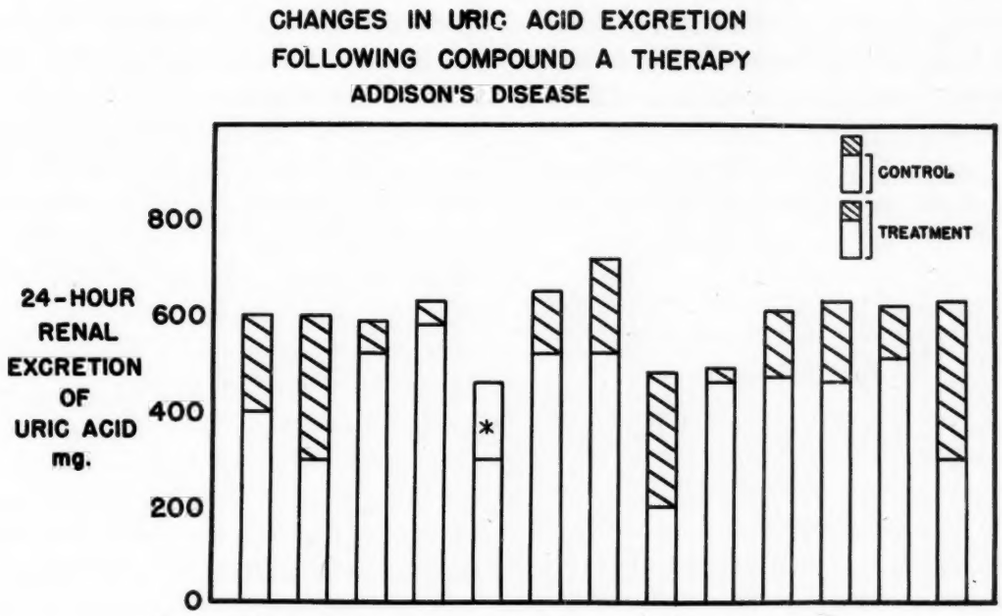

FIG. 3. *Uric acid excretion decreased in this case by the amount indicated.*

being 190 mg. of *creatine* daily during the control period (range 140 to 300 mg.). On Compound A (20 to 30 mg. daily) there was a moderate increase in creatine excretion in three of the four patients, the average increase amounting to 60 mg. daily. Concurrently, creatinine excretion rose from an average of 770 mg. daily to 910 mg. daily.

Glycocyamine excretion was studied in two patients during a three-day period on 30 mg. of Compound A. No significant change was noted, the excretion being 57 mg. daily during a control period as opposed to 54 mg. daily on Compound A for patient M. T. For patient J. P. the values were 24 and 21 mg. of glycocyamine for control and treatment periods, respectively.

A summary of the over-all changes in renal excretion is presented in Table IV. A significant increase in the renal excretion of inorganic phosphorus occurred only in those experiments in which an increase in the daily excretion of total nitrogen exceeded 1.0 Gm. In the majority of experiments the increase in potassium and inorganic phosphorus excretion exceeded the theoretical quantity of these substances which would have been derived from body protein calculated on the basis of the concomitant increase in urinary nitrogen.[35] Thus phosphorylating mechanisms would appear to undergo changes together with, but not quantitatively related to, the nitrogen and potassium loss under the influence of Compound A. In general, an increase in the excretion of potassium, inorganic phosphorus and total nitrogen occurred more regularly when larger doses of Compound A were employed (Table IV); whereas sodium and chloride retention occurred with approximately the same frequency in both the large and small-dose experiments.

TABLE IV
SUMMARY OF CHANGES IN RENAL EXCRETION ASSOCIATED WITH 11-DEHYDROCORTICOSTERONE ACETATE THERAPY

Daily Dose of Compound A, mg.	Number of Experiments	Per Cent of Patients Showing				
		Decreased Na Excretion	Decreased Cl Excretion	Increased K Excretion	Increased P Excretion	Increased N Excretion
10–15	4	100	100	50	25	75
20–60	10	90	100	90	80	90

The two patients (J. P. and H. J.) who showed little or no change in the urinary excretion of nitrogen, phosphorus and potassium had both had a nephrectomy previously. In patient J. P. the glycocyamine excretion was approximately half that observed in the patients with two kidneys.

URINARY 17-KETOSTEROID EXCRETION AND VARIATIONS IN CORTICOSTEROID-LIKE SUBSTANCES

Urinary 17-ketosteroid excretion was followed in five instances.* A small increase in the average value was observed during Compound A treatment (10 to 60 mg. daily for three to five days). The average daily excretion for the group amounted to 2.4 mg. in the control period and rose to 3.1 mg. on treatment with Compound A administered alone or in addition to a basal, constant amount of desoxycorticosterone acetate.

Urinary corticosteroid-like substances were determined prior to and during Compound A therapy (10 to 60 mg. daily for three to five days) in twelve instances.† The average value during the control period was 0.23 mg. per day (0.25 mg. for the group with known tubercular etiology of Addison's disease, 0.23 mg. for those of unknown etiology). During Compound A therapy the average value was 0.25 mg. per day. According to Talbot's experience these values fall within the low range of normal. In the normal control (T. H.) given 45 mg. of Compound A for three days the corticosteroid-like substances fell from 0.28 to 0.19 mg. per day, and the 17-ketosteroid output rose from 11.4 to 15.6 mg. per day.

FECAL NITROGEN AND FAT EXCRETION

Because of the clinical impression that patients on Compound A tended to show a somewhat drier stool, a number of three-day stool collections were analyzed for nitrogen, fat and fatty acids.

Patient R. G. on a constant diet of 250 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat had a 30 per cent decrease in dry weight of the average daily stool while she was receiving 30 mg. of Compound A daily. At the same time the fecal nitrogen fell from 1.4 to 0.9 Gm. daily, a 37 per cent decrease. During this period an increase in urinary nitrogen excretion of 1.2 Gm. daily was observed. Thus the possibility is presented that some of the increase in urinary nitrogen excretion was related to the improved intestinal absorption.

A marked decrease in the output of both fat and fatty acids amounting on the average to 60 per cent of the control values, or about twice the percentage decrease in dry weight, indicated greater fat assimilation under Compound A treatment (three cases).*

From these preliminary observations it would appear that Compound A leads to the formation of somewhat drier, less bulky stools and to a decrease in the average daily nitrogen, fat and fatty-acid excretion in the stool.

EFFECT OF 11-DEHYDROCORTICOSTERONE ACETATE ON BLOOD CONSTITUENTS

A summary of the blood changes in the patients who received 20 mg. or more of Compound A daily for two to five days is presented in Table v. A slight increase in the total white count was noted in conjunction with a small decrease in the per cent of lymphocytes. The total lymphocyte count for the group, however, showed no significant change.

There was a consistent decrease in the fasting serum inorganic phosphorus level, especially with doses over 20 mg. of Compound A daily. (Table vi.)

* We wish to thank Dr. F. Albright and Miss E. Callow for carrying out the 17-ketosteroid determinations.[36]

† We are indebted to Dr. N. B. Talbot for the estimation of corticosteroid-like substances in the urine by his colorimetric method.[37]

* We are indebted to Dr. R. A. Lewis for the fecal fat determinations.

Plasma amino acid levels increased to the accepted normal[38] in patients with a low initial level. There was no further rise on Compound A in patients who showed normal levels during the control period. (Table VII.)

TABLE V
SUMMARY OF CHANGES IN BLOOD CONSTITUENTS FOLLOWING 11-DEHYDROCORTICOSTERONE ACETATE THERAPY* IN PATIENTS WITH ADDISON'S DISEASE

	Number of Experiments	Control value	Value Following Rx
Change in body weight kg./day	11	−0.2	0
Hematocrit % R.B.C. volume	13	41	39
Total serum protein gm./100 cc	10	6.7	6.8
Serum sodium m.eq./L.	11	139	140
Serum chloride m.eq./L.	12	105	105
Serum potassium m.eq./L.	11	5.4	5.2
Serum inorganic phosphorus m.M./L.	12	1.2	1.2
Serum CO_2 combining capacity m.eq./L.	12	25.4	25.2
Blood sugar mg./100 cc.	12	83	84
Blood urea nitrogen mg./100 cc.	12	16	15
Plasma alpha amino acid nitrogen mg./100 cc.	8	3.9	4.3
Serum uric acid mg./100 cc.	7	4.8	4.7
Blood pyruvate mg./100 cc.	6	0.87	0.82
Serum cholesterol mg./100 cc.	9	183	171
% free		26	26
Urea clearance % normal	10	75	74
Total W.B.C. per c. mm.	13	6900	7000
Per cent lymphocytes	13	53	50
Total lymphocyte count per c. mm	13	3660	3500

* The average daily dose of Compound A was 30 mg. per day (range 20–60 mg.).

EFFECT OF 11-DEHYDROCORTICOSTERONE ACETATE ON CARBOHYDRATE METABOLISM

In studying the effect of adrenal steroid therapy on carbohydrate metabolism it is important to differentiate those changes which are primary from those which follow secondarily upon improvement in the clinical condition. Patients treated with desoxycorticosterone acetate may, as a consequence of improved clinical condition, greatly increase their dietary intake. It is possible for the fasting blood sugar level to increase merely as a result of the change in diet (J. P.). [Table VIII.] It is apparent that the change observed in carbohydrate metabolism under these circumstances does not represent a specific effect of desoxycorticosterone acetate therapy.

TABLE VI
CHANGES IN SERUM INORGANIC PHOSPHORUS LEVELS FOLLOWING COMPOUND A THERAPY (30 MG. DAILY)

Patient	Serum Inorganic Phosphorus m. M./L.	
	Control	Following 2–5 Days of Compound A Therapy
R. G.	1.2	1.0
W. C.	1.1	1.0
K. K.	1.5	1.4
J. P.	1.1	1.0
M. N.	1.6	1.5
M. T.	1.9	1.7
M. F.	1.1	1.1
K. K. (60 mg.)	1.3	1.4

TABLE VII
CHANGES IN PLASMA AMINO ACID LEVEL DURING COMPOUND A THERAPY

Patient	Dose Hormone, Mg.	Control Value	Value during Therapy
		Mg. Alpha Amino Nitrogen Per Cent	
E. H. ♀	20	2.4	4.2
J. P. ♂	30	4.2	4.1
J. P. ♂	30	4.2	4.0
M. T. ♀	30	4.6	4.2
K. K. ♂	30	4.8	4.3
V. A. ♀	30	3.4	4.4
J. P. ♂	45	3.5	4.5
K. K. ♀	60	4.5	4.2
		Average value 3.9	Average value 4.3

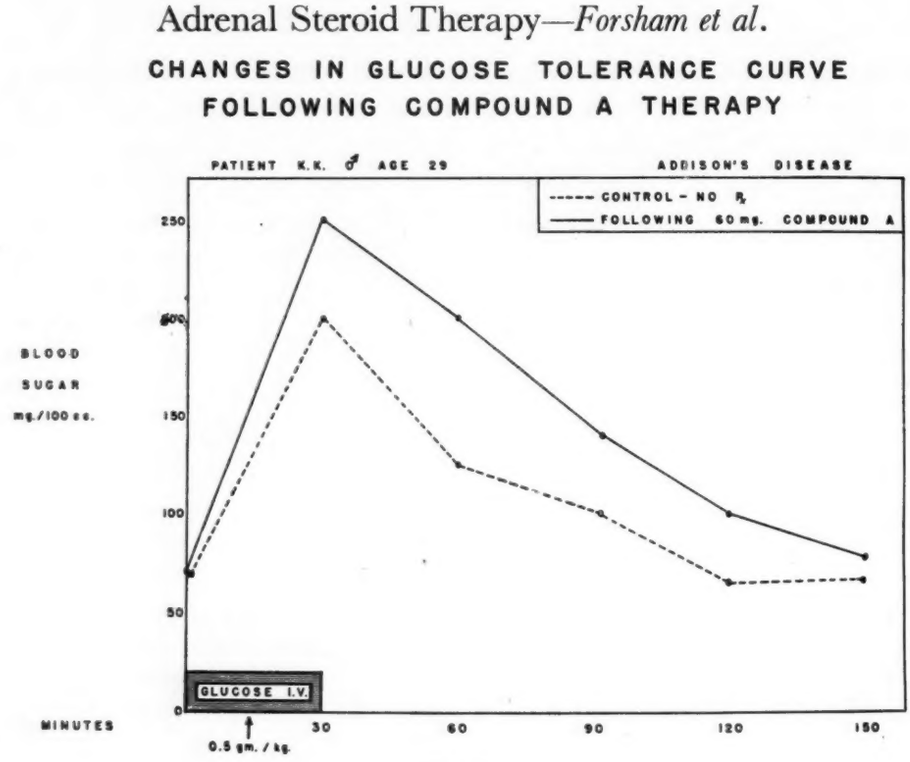

FIG. 4

In the present studies it is important to point out that patients were maintained on a constant diet throughout the period of observation. Hence improvement which might follow an increased appetite and intake of food is thereby obviated.

TABLE VIII
THE EFFECT OF INCREASE IN DIETARY CARBOHYDRATE AND CALORIES ON THE FASTING BLOOD SUGAR—PATIENT J. P.

	High-Fat, Low-Carbohydrate Diet	Standard Diet	High-Carbohydrate Diet
Carbohydrate Gm. daily	60	230	675
Protein Gm. daily	57	81	53
Fat Gm. daily	110	44	90
Calories	1450	1640	3750
Fasting blood sugar	66	78	95

Fasting Blood Sugar. The average values for the group did not change significantly on Compound A therapy. (Table v.)

Intravenous Glucose Tolerance Test. Studies were made on three patients during a control period and during a period of Compound A therapy (30 mg. or more daily). In two of the patients (M. F. and J. P.) no appreciable change in the glucose tolerance curve was observed as a consequence of Compound A therapy for two to three days prior to the test. Patient J. P. received 30 mg. daily and patient M. F. 45 mg. daily. The clinical condition of both patients at the termination of the test, however, was much better, and no late hypoglycemic manifestations were observed. Patient K. K. received 60 mg. of Compound A daily for three days. A definite elevation of the glucose tolerance curve occurred in this case. (Fig. 4.) It is to be noted that this patient's basal metabolic rate was minus 27 per cent and there were clinical signs of associated hypothyroidism.

Blood Pyruvate. The average value for fasting blood pyruvate level did not change appreciably during the period on Compound A therapy. (Table v.) Changes in pyruvate levels were followed during the course of the intravenous glucose tolerance

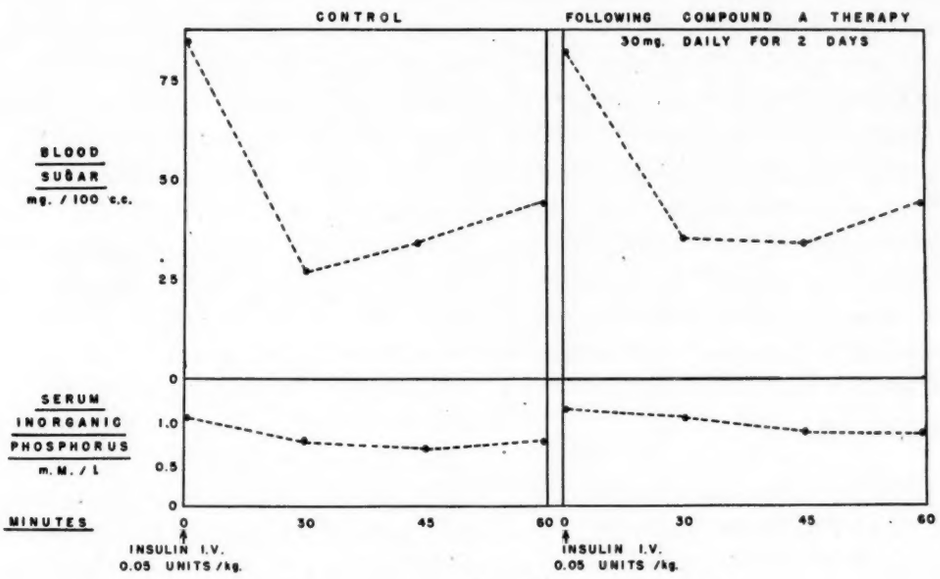

FIG. 5

test in three patients. In two patients (M. F. and J. P.) given the control intravenous glucose tolerance test an average rise of 45 per cent in blood pyruvate level was noted; while during the glucose tolerance test with Compound A therapy a 24 per cent rise in blood pyruvate was observed. In patient K. K. on Compound A blood pyruvate level during the glucose tolerance test did not change significantly over the control.

Inorganic Serum Phosphorus. There appeared to be a slight but consistent decrease in serum inorganic phosphorus level in those patients who received 30 mg. or more of Compound A daily, although the average value for the fourteen experiments showed no significant difference. (Tables V and VI.) Serum inorganic phosphorus level was followed during the intravenous glucose tolerance test in three patients (M. F., K. K., and J. P.). Determinations were made at thirty-minute intervals, after the end of the infusion and the mean value for four determinations was calculated. In two patients a significant decrease in the average value for serum inorganic phosphorus was observed during the intravenous glucose tolerance test. No change was noted in patient K. K. (Table IX.)

TABLE IX

EFFECT OF COMPOUND A ON CHANGES IN INORGANIC SERUM PHOSPHORUS FOLLOWING INTRAVENOUS GLUCOSE ADMINISTRATION

Patient	Inorganic Serum Phosphorus m.M./L. Mean of Four Determinations during Intravenous Glucose Tolerance Test	
	Control (No Treatment or Desoxycorticosterone Acetate)	Treatment (Compound A)
J. P.....	0.76	0.59
M. F.....	1.07	0.83
K. K.....	1.23	1.23

Insulin Tolerance Test.[39] The effect of insulin administered intravenously was studied in one patient during a control period and later after 30 mg. of Compound A had been given daily for two days. In both instances the patient experienced a mild hypoglycemic attack which was symptomatically

less severe on Compound A and followed by a more rapid return to normal. No biochemical difference in response to insulin was observed. (Fig. 5.)

Basal Metabolic Rate and Respiratory Quotient. After three to five days of treatment with Compound A in dosages varying from 10 to 45 mg. daily no consistent change in respiratory quotient or in basal metabolic rate was observed in the six patients in whom these determinations were made. These results may be inconclusive because of the small series and the fact that several of the patients were not ideal subjects for studies of respiratory metabolism.

EFFECT OF 11-DEHYDROCORTICOSTERONE ACETATE ON NEUROMUSCULAR FUNCTION

Great improvement in work capacity has been observed in patients with Addison's disease treated with desoxycorticosterone acetate.[1] In most instances this improvement may be accounted for by an increase in plasma volume and blood pressure, restoration of fluid balance, and normal serum sodium, chloride and potassium levels. Patients treated with desoxycorticosterone acetate alone, however, rarely have their muscle strength restored completely to normal. These clinical observations confirm those of Ingle on the work performance of adrenalectomized rats treated with the same compound. In animal experiments[40] it has been demonstrated that whole adrenal extract treatment or the use of adrenal steroids with an oxygen atom in the carbon-11 position is capable of inducing much greater muscular response than is the case with desoxycorticosterone. It has been our impression clinically that *continued* therapy with *adequate* doses of adrenal cortical extract or Upjohn's Lipo-Adrenal Cortex has resulted in further improvement in the muscular strength of patients maintained on a basic dose of desoxycorticosterone acetate. Similar observations have been reported by MacBryde.[8]

While there is little difficulty in obtaining unequivocal evidence of improvement in muscle function when one treats a bedridden patient with Addison's disease with desoxycorticosterone acetate (daily injections or pellet implantation), it is difficult to demonstrate conclusively *additional* improvement in a patient who is up and about and already in fairly good physical condition. Under these circumstances it is important to avoid errors which may result from interpretation of the patient's description of his improvement (subjective evaluation) or from using a muscle test in which the factor of motivation plays a significant rôle (weight pull-up tests, "step-up" tests, treadmill, etc.). For this reason we have attempted to standardize an "objective" method of measuring neuromuscular response by stimulating electrically the ulnar nerve and by recording the subsequent contractions of the ulnar muscle group. (See Methods.)

With this test it was impossible to demonstrate any significant increase in the rate of stimulation which induced fatigue in patients treated from one to five days with Compound A alone, dose range 10 to 30 mg. daily. Furthermore, in a single patient (K. K.) no change was observed following Compound F, 15 mg. daily for three days, or following the injection of 50 cc. of Eschatin (a single dose) intravenously, the test being run two hours after the infusion.

Improvement in response to the test was observed in patients treated with desoxycorticosterone acetate during a period in which marked sodium and chloride retention had occurred with weight gain. Improvement in response to the test was also observed when Compound A treatment was added to a basic maintenance dose of desoxycorticosterone acetate. Again under the latter circumstance, significant sodium

and chloride retention with weight gain was observed.

Thus, in untreated or in inadequately treated patients hormone therapy which induces striking salt and water retention will result in an improvement in neuromuscular function, but it has not been possible to demonstrate this by the above method in the absence of these changes.

EFFECT OF 11-DEHYDROCORTICOSTERONE ACETATE ON REACTIONS TO DIETARY STRESS

Previous studies[9] have shown that patients with Addison's disease cannot maintain a normal fasting blood sugar level when fed a diet composed largely of protein and fat although of adequate caloric content. Patients with Addison's disease also develop hypoglycemic symptoms readily during a moderately prolonged fast. Thus, the inability to maintain adequate gluconeogenesis or to increase the utilization of fat can be brought out best by a diet high in protein and fat but low in carbohydrate. To that end we have devised one experiment in which we fed diets of constant caloric composition but varying fat and carbohydrate contents for identical time intervals. With this and periods of prolonged fasting we have attempted to test the efficacy of Compound A under conditions of stress.

Low-Carbohydrate, High-Protein, High-Fat Diet. Patient J. P., when studied in 1939, developed a hypoglycemic crisis on a diet adequate in calories but relatively low in carbohydrate.[9] During the present study he was fed a diet almost identical to that employed in 1939. He was observed during two periods of four days each on this diet, one a control period without treatment, one with Compound A therapy, 45 mg. daily. Care was taken that the dietary intake for several days prior to each test period was identical on the two occasions. During the four days on the low-carbohydrate diet without Compound A the patient experienced hypoglycemic episodes on two mornings which necessitated the administration of supplementary carbohydrate. During the four days on the same diet but while receiving 30 mg. daily of Compound A this patient had no hypoglycemic episodes. A small but definite increase in the average fasting blood sugar level occurred, the value during the control period being 66 mg. per 100 cc. and during the Compound A period 77 mg. per 100 cc. On one occasion during therapy a blood sugar level of 60 mg. per 100 cc. was attained. No symptoms were manifest at this time, although symptoms had developed in the same patient with an identical level of blood sugar during the control period without treatment. An increase in the threshold for hypoglycemic manifestations following whole adrenal extract therapy has been noted repeatedly in patients with Addison's disease as well as in adrenalectomized dogs.[40]

Prolonged Fasting. Patient R. G. fasted for twenty-four hours on two occasions. During one period placebo injections were given throughout. Between the twentieth and twenty-fourth hours this patient became very hungry, and at the conclusion of the fast (twenty-four hours) she developed a severe hypoglycemic crisis which necessitated vigorous intravenous therapy. On the second occasion, the patient was treated with Compound A, 30 mg. daily for two days, prior to the fast and throughout the day of the fast. The hormone was given at the rate of 5 mg. every four hours. During this prolonged fast the patient did remarkably well and at the conclusion of the test drank fruit juice and ate readily. No crisis ensued. A study of the blood sugar during the two experiments (Fig. 6) indicates little change until after the twentieth hour of the fast at which time a definite change in blood sugar levels occurred, a higher level being

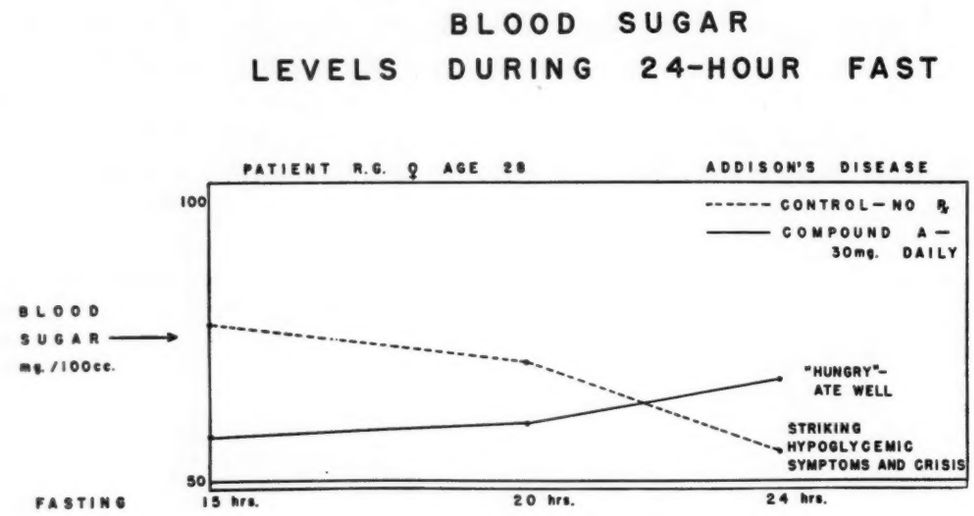

FIG. 6

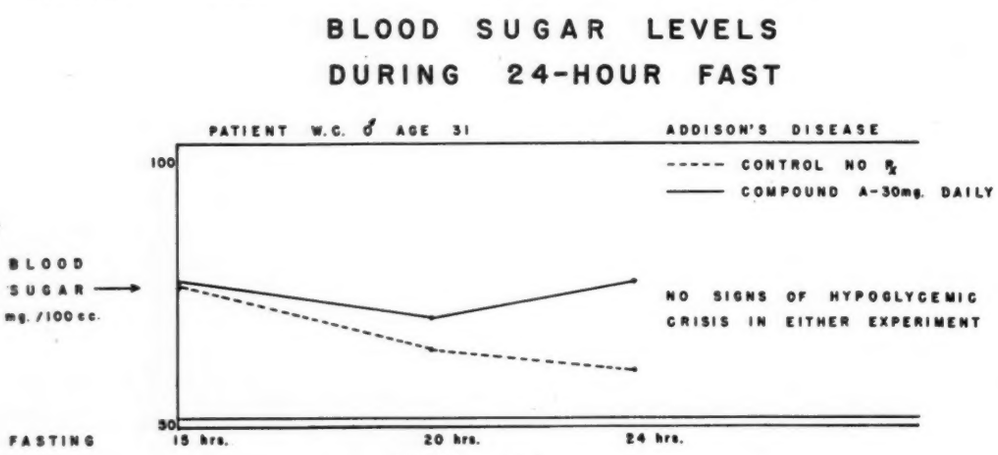

FIG. 7

FIGS. 6 and 7

maintained during the fast when Compound A was administered.

Patient W. C. underwent a similar period of fasting. This patient was able to tolerate twenty-four hours of fasting without developing hypoglycemic crisis during the control experiment without treatment. Since it was not believed advisable to extend the fast beyond twenty-four hours, no critical clinical differentiation could be established between the control fasting period and a twenty-four hour fast on Compound A therapy. The blood sugar values, however, showed distinctly higher levels during the last twenty-four hours of the fast on Compound A therapy. (Fig. 7.) The magnitude of the changes in blood sugar level between the twentieth and the twenty-fourth hours of fasting on Compound A therapy were similar to those which have been observed in patients treated with 50 cc. of aqueous adrenal extract.[9] Unfortunately, it was not possible to study the rate of nitrogen excretion in these two patients during the prolonged fast with and without Compound A.

A similar experiment was carried out on a third patient (V. A.). These observations are summarized in Figure 8. This patient developed a severe hypoglycemic crisis at about the twentieth hour of a prolonged fast; it was necessary to discontinue the experiment at this time and institute intravenous therapy. The blood sugar attained the low value of 35 mg. per 100 cc. Treatment with Compound A was then begun, 75 mg. being given on the day of the crisis

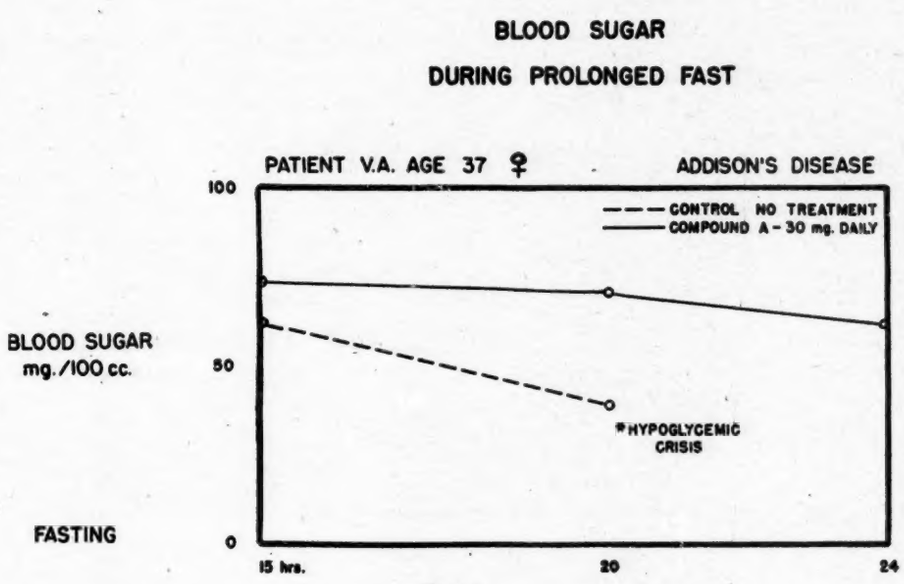

FIG. 8

and 30 mg. daily thereafter. On the third day after the preceding crisis, while being maintained on 30 mg. of Compound A daily, this patient fasted again and experienced no difficulty throughout the twenty-four hour fast. Blood sugar levels were much higher and the clinical condition of the patient remained satisfactory. During the earlier period of the fast the urinary nitrogen excretion was actually lower under Compound A therapy than in the control test. Nitrogen excretion was well sustained, however, throughout the whole period of the fast on Compound A. At no time did a decrease in nitrogen output occur, comparable to that previously noted in patients with untreated Addison's disease during prolonged fasting.[9]

STUDIES ON A NORMAL SUBJECT

Subject T. H., a twenty-four year old healthy white male, was maintained on a constant diet of 300 Gm. carbohydrate, 72 Gm. protein and 92 Gm. fat throughout this study. He was allowed to carry on his usual activities as a medical student. The subject was allowed water ad libitum. He was maintained on the constant diet for a total period of six days before Compound A was administered. It appeared from weight changes and urinary excretion during the control period that the control standard diet was slightly inadequate in total calories.

The subject was given 45 mg. of Compound A daily for three days, 15 mg. being given intramuscularly every eight hours. During the period of treatment the subject experienced no unusual reactions; in contrast to weight loss during the control period, however, the subject maintained his weight during the period of Compound A administration (Fig. 9), weight loss occurring again during a control period after hormone administration had been discontinued. The changes in weight probably reflect the changes in sodium and chloride balance, since a definite retention of sodium and chloride occurred during the period on Compound A and increased sodium and chloride loss followed its withdrawal. Nitrogen excretion during Compound A therapy was not increased over the average value during the preliminary control period but was greater than that observed during the subsequent control period. Potassium and inorganic phosphorus showed only small increases. Thus, during a period in which the

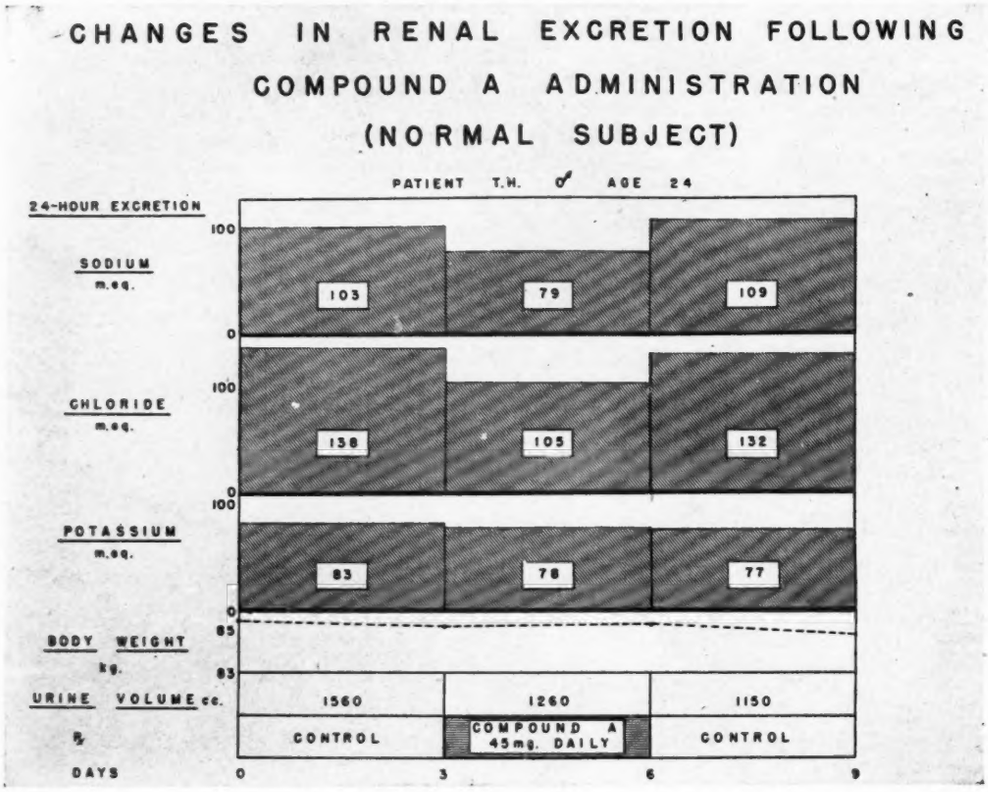

FIG. 9

patient was receiving a reasonably adequate diet, the only significant changes in balance were those of sodium and chloride retention. Seventeen-ketosteroid excretion rose from 11.4 mg. per twenty-four hours to 15.6 mg., and corticosteroid-like substances fell from 0.28 mg. to 0.19 mg. per twenty-four hours.

At the conclusion of both treatment and control periods the subject was given an intravenous glucose tolerance test after an over-night fast. At the termination of the intravenous glucose tolerance test (150 minutes), an intravenous infusion of epinephrine (1 mg.) in 500 cc. of normal saline was given at a constant rate so that the total dose (1 mg.) was administered in exactly two hours.

During Compound A therapy the intravenous glucose curve was slightly but not significantly higher than during the control period. (Fig. 10.) In contrast to the regularly greater reduction of the serum inorganic phosphorus levels which was observed in the patients with uncomplicated Addison's disease during intravenous glucose administration while on Compound A therapy, normal subject T. H. showed higher average serum inorganic phosphorus values throughout the intravenous glucose tolerance test while on Compound A.

With the administration of epinephrine there was a marked rise in blood sugar and pyruvate levels and a concomitant decrease in serum inorganic phosphorus. The blood sugar rise with and without Compound A following epinephrine infusion was practically identical (Chart 10). No significant difference in the blood pyruvate level was observed in the two experiments. The decrease in serum inorganic phosphorus during epinephrine infusion was somewhat greater during the control period than with Compound A treatment. No difference in

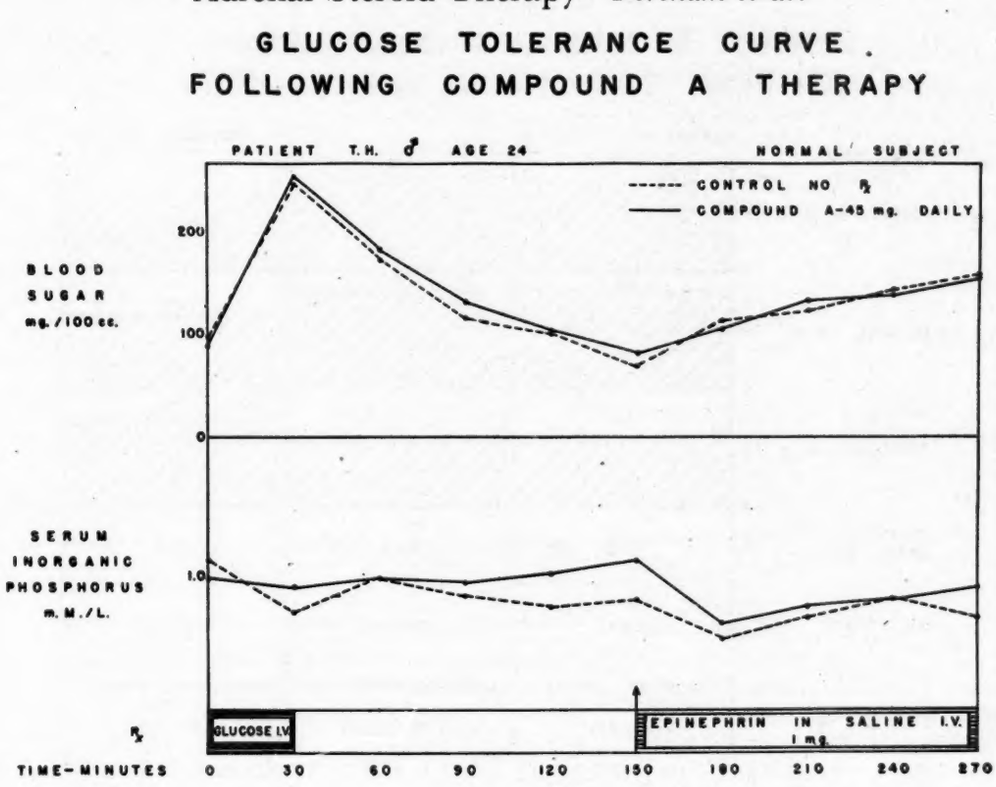
GLUCOSE TOLERANCE CURVE.
FOLLOWING COMPOUND A THERAPY
PATIENT T.H. ♂ AGE 24
NORMAL SUBJECT
CONTROL NO Rx
COMPOUND A-45 mg. DAILY
BLOOD SUGAR mg./100 cc.
200
100
0
SERUM INORGANIC PHOSPHORUS m.M./L.
1.0
Rx
GLUCOSE I.V.
EPINEPHRIN IN SALINE I.V. 1 mg.
TIME-MINUTES
0 30 60 90 120 150 180 210 240 270

FIG. 10

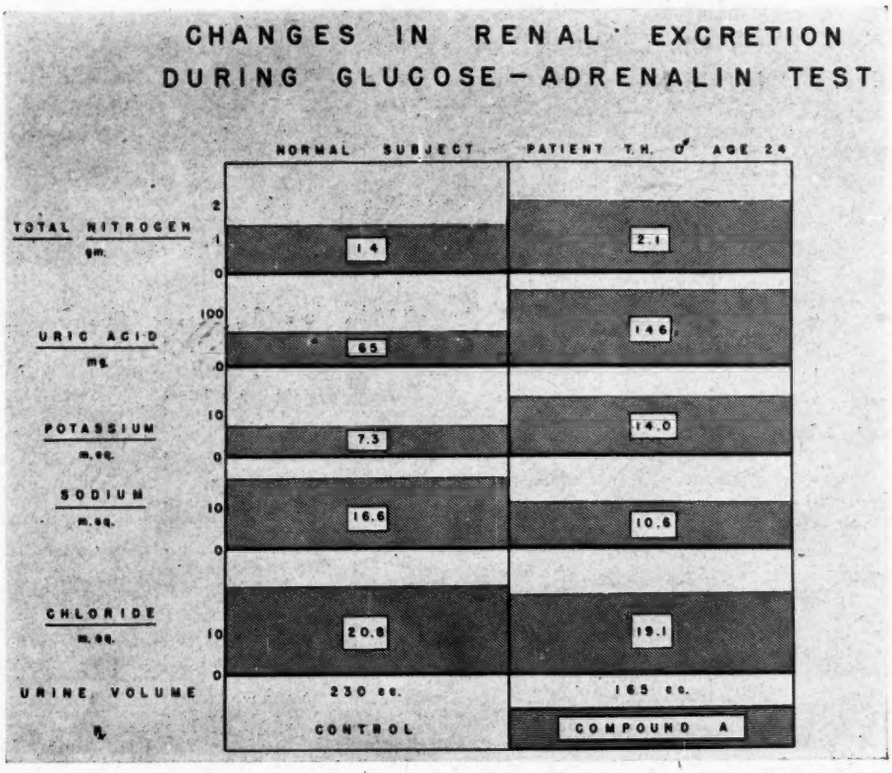
CHANGES IN RENAL EXCRETION
DURING GLUCOSE-ADRENALIN TEST
NORMAL SUBJECT
PATIENT T.H. ♂ AGE 24
TOTAL NITROGEN gm.
2
1
0
1.4
2.1
URIC ACID mg.
100
0
65
146
POTASSIUM m.eq.
10
0
7.3
14.0
SODIUM m.eq.
10
0
16.6
10.6
CHLORIDE m.eq.
10
0
20.6
19.1
URINE VOLUME
230 cc.
165 cc.
Rx
CONTROL
COMPOUND A

FIG. 11

EFFECT OF ADRENAL STEROID THERAPY
ON RENAL EXCRETION OF ELECTROLYTES

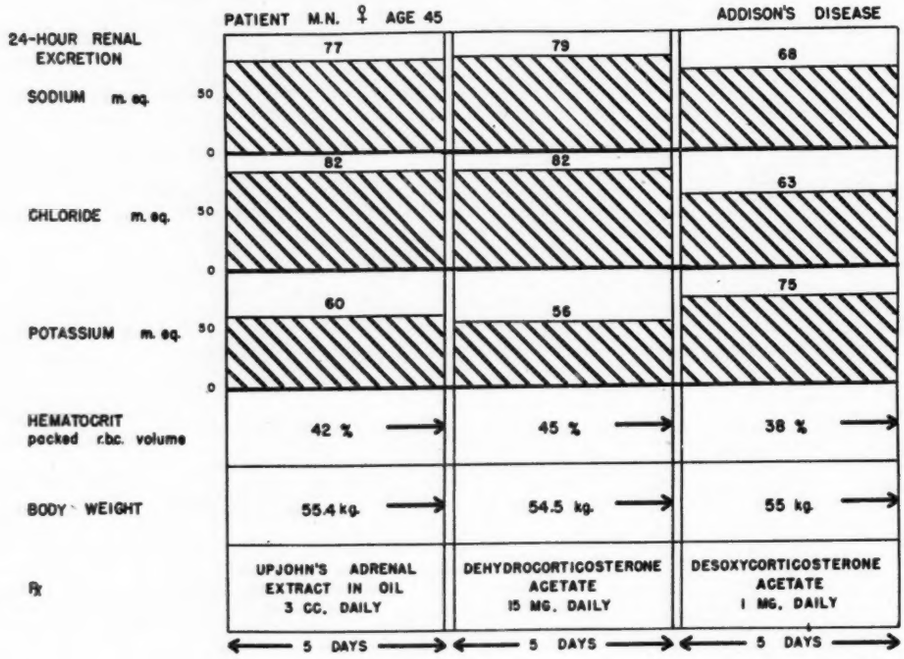

FIG. 12

EFFECT OF COMBINED ADRENAL STEROID THERAPY
ON RENAL EXCRETION OF ELECTROLYTES

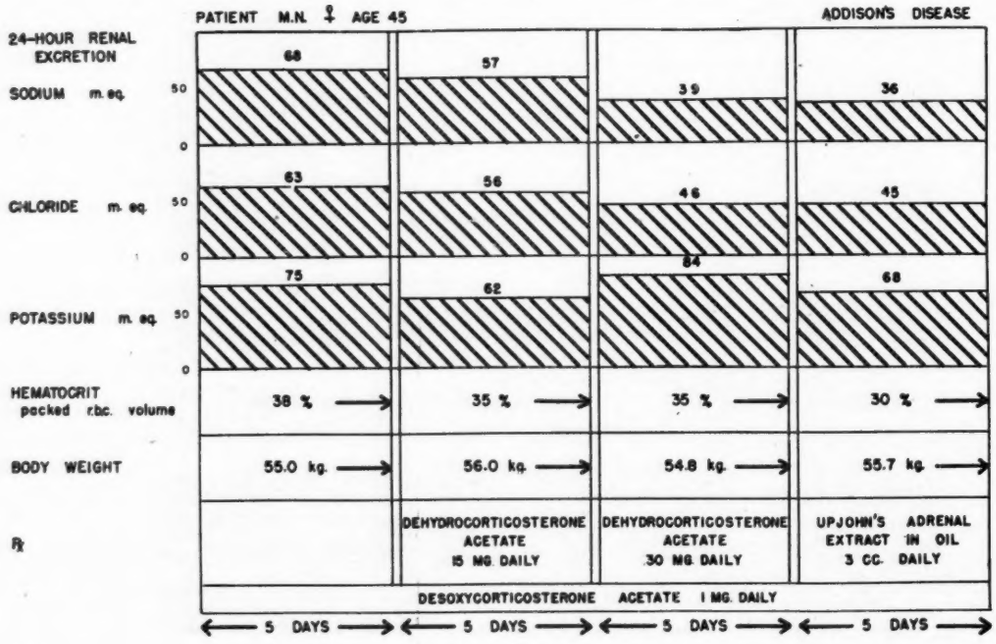

FIG. 13

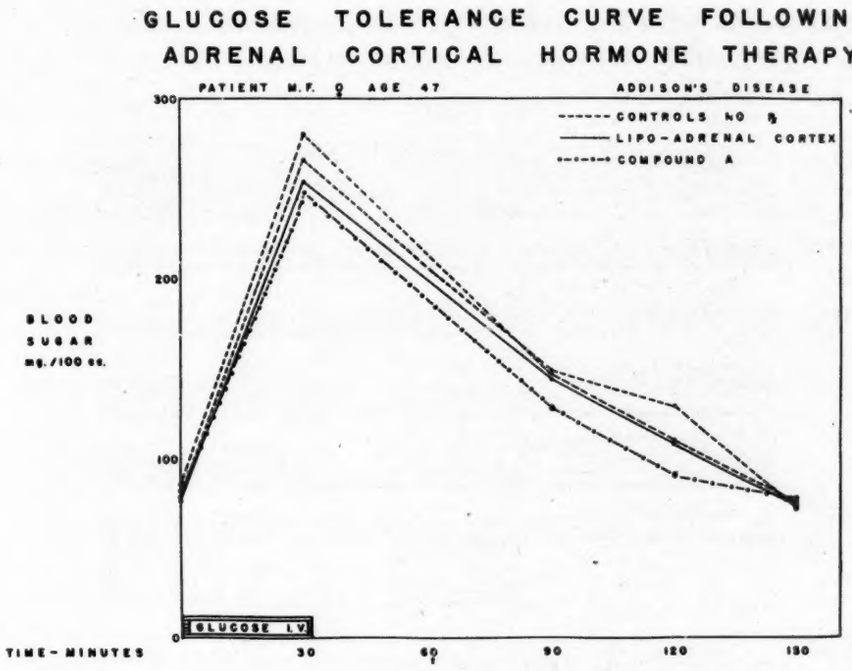

FIG. 14

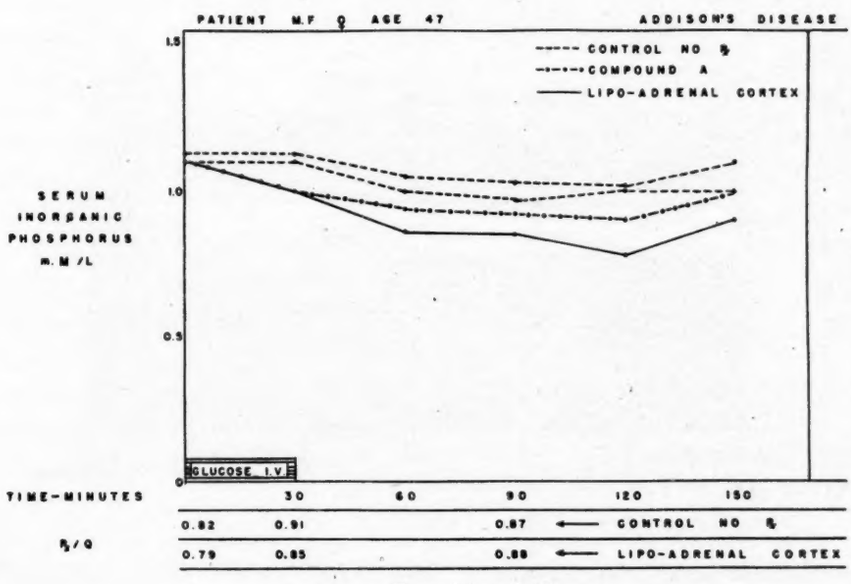

FIG. 15

FIGS. 14 and 15

clinical response to epinephrine was noted in the two instances.

Urinary excretion during the four and one-half hour test period showed a remarkable change with Compound A therapy. (Fig. 11.) Total nitrogen, uric acid and potassium excretion were increased, while sodium excretion was decreased. Chloride excretion remained constant and was approximately equal to the sum of the values for sodium and potassium in the two experiments.

During the period on Compound A therapy (45 mg. daily) no significant changes

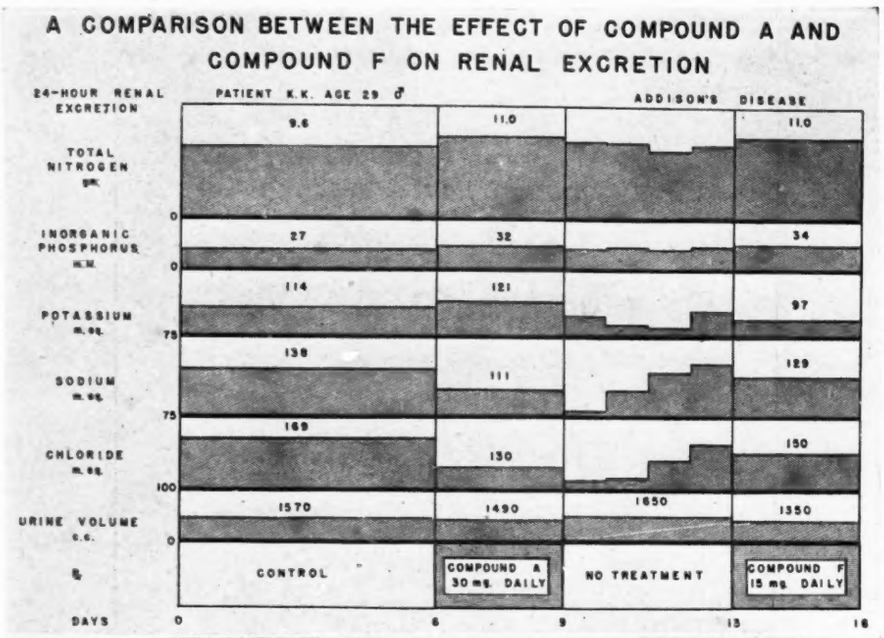

FIG. 16

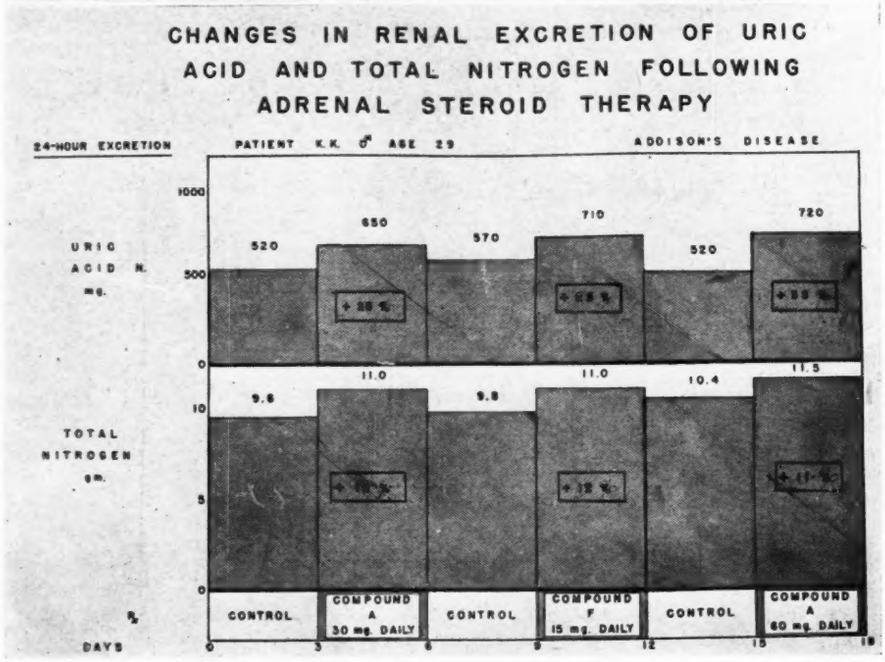

FIG. 17

FIGS. 16 and 17

occurred in the following blood constituents: Hematocrit, total serum protein, serum chloride, serum potassium, carbon dioxide combining power, cholesterol, blood sugar and blood urea nitrogen. Inorganic serum phosphorus fell from 1.5 m.M./1. to 1.0 m.M./1., and total white count decreased from 7,000 to 5,600, the percentage lymphocytes changing from 37 to 36 per cent. The serum uric acid rose from 4.5 to 5.4 mg. per cent.

COMPARISON BETWEEN THE EFFECT OF SYNTHETIC 11-DEHYDROCORTICOSTERONE ACETATE AND NATURAL LIPO-ADRENAL CORTEX

From studies on several patients it appears that 15 to 30 mg. of Compound A is equivalent in its sodium and chloride-retaining effect to that observed with 3 to 6 cc. of Lipo-Adrenal Cortex. In both instances one-third of the total daily dose was

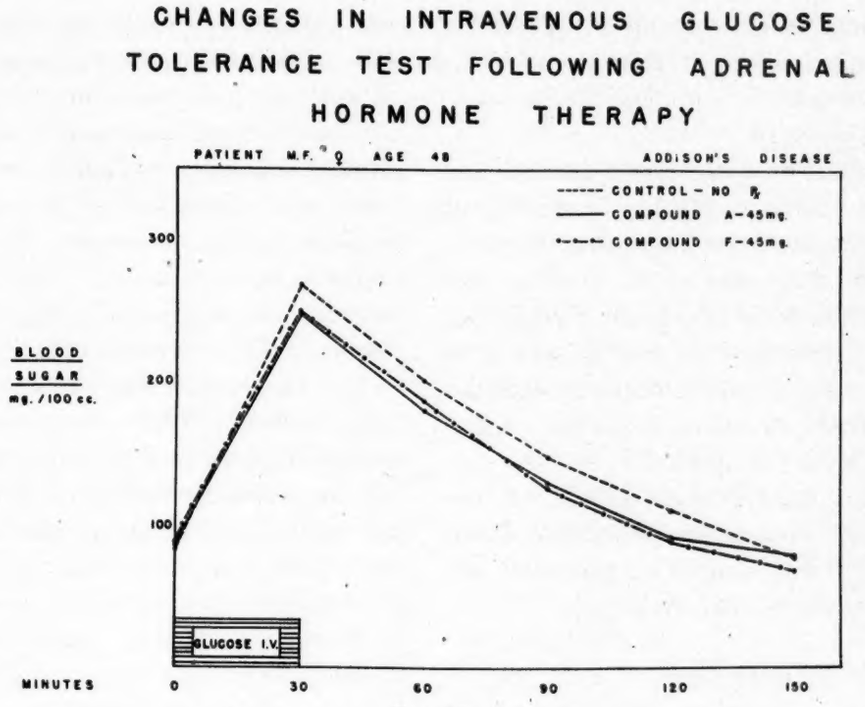

FIG. 18

administered every eight hours. A comparison of these effects in patient M. N. is shown in Figure 12. These quantities of Compound A and Lipo-Adrenal Cortex appear approximately equivalent in effect to 0.5 to 1 mg. of desoxycorticosterone acetate in sesame oil, the latter given as a single daily injection.

The sodium chloride retaining effect of both Compound A and Lipo-Adrenal Cortex proved additive when given to a patient receiving a basic dose of desoxycorticosterone acetate. (M. N., Fig. 13.)

The increase in nitrogen excretion following 15 to 30 mg. of Compound A is approximately the same as that observed after 3 to 6 cc. of Lipo-Adrenal Cortex.

Compound A (30 mg. daily) and Lipo-Adrenal Cortex (6 cc. daily), given two to three days prior to the test, led to apparently identical effects on the intravenous glucose tolerance curve (Fig. 14) which may be summarized as follows: (1) No essential change in fasting blood sugar; (2) no consistent change in glucose tolerance; (3) a lowered fasting serum inorganic phosphorus level with a more marked decrease during the tolerance test (Fig. 15); (4) elimination of reactive hypoglycemia toward the end of the test, although the blood sugar values were occasionally as low as in the hypoglycemic episode during the control test. Both preparations in adequate dosage ameliorated or prevented hypoglycemic reactions during prolonged fasting in patients with Addison's disease.

COMPARISON BETWEEN THE EFFECT OF SYNTHETIC 11-DEHYDROCORTICOSTERONE ACETATE AND NATURAL 17-HYDROXYCORTICOSTERONE

Studies on patient K. K. indicated that 15 mg. of Compound F had little influence on sodium chloride retention when administered in a dosage of 2.5 mg. in aqueous solution every four hours. (Fig. 16.) While potassium excretion increased with Compound A, it actually decreased with Compound F.

The increase in nitrogen excretion and uric acid output is approximately of the same magnitude for 30 mg. of Compound A

as for 15 mg. of Compound F. (Fig. 17.) The prolonged effect of Compound A in oil is shown well in the "No Treatment" period in Figure 16.

The response to intravenous glucose was changed in analagous fashion by 45 mg. of both Compound A and Compound F given prior to the test in patient M. F. (Fig. 18.) The serum inorganic phosphorus fell 22 per cent with Compound A and 27 per cent with Compound F when compared with the control period. Pyruvate levels rose somewhat more with Compound F.

There was no difference in clinical behavior noted between the periods on Compound A (30 mg.) and Compound F (15 mg.) for the short-term trials.

COMMENTS

The administration of Compound A during the short-term metabolic experiments does not permit one to draw a final conclusion as to the ultimate efficacy of synthetic 11-dehydrocorticosterone acetate in the treatment of patients with Addison's disease. For this reason a group of patients is being carried on this preparation for a prolonged period. Unfortunately, the large amount of hormone which is required for extended therapy will necessarily limit the size of the group. Another limitation to long continued therapy with the present preparation of Compound A in sesame oil is the large quantity of the solvent which must be injected intramuscularly (6 cc. daily of sesame oil) if 30 mg. of the material is used. An attempt was made to decrease the quantity of the solvent by employing propylene glycol. By this method it was possible to obtain a concentration of 15 mg. of Compound A per cc. Unfortunately, local reactions were encountered in the three patients in whom this preparation was tried.

Factors which were responsible for the selection of the dosage employed in most of the patients (20 to 30 mg. daily) were (1) the technical difficulty encountered in administering more than 6 cc. (30 mg.) of the oil solution intramuscularly daily, (2) the limited quantity of hormone which had been synthesized and (3) a knowledge that clinical usefulness would be exceedingly limited, because of the high cost of the preparation, if quantities larger than 15 to 30 mg. daily were required.

In patients with Addison's disease sodium and chloride retention with desoxycorticosterone acetate therapy is accompanied by an increased excretion of potassium and inorganic phosphorus not associated with any significant change in the renal excretion of nitrogen.[41]

In the present study two factors may play a rôle in the increased potassium and inorganic phosphorus excretion which was observed in eleven of fourteen experiments: (1) The sodium and chloride retaining effect of Compound A and a transient increase in potassium and inorganic phosphorus excretion on this basis and (2) increased potassium and inorganic phosphorus made available as the result of tissue breakdown. This is supported by the concomitant increase in total nitrogen and uric acid excretion without any appreciable change in serum potassium and inorganic phosphorus levels despite appreciable losses in the urine.

Although an increase in urinary nitrogen excretion was observed in twelve of the fourteen experiments, it is important to note that the magnitude of this change was rather small, i.e., 1.2 Gm. daily. It is possible that a small amount of nitrogen was made available for excretion by virtue of increased absorption of nitrogen from the gastrointestinal tract. Our studies on patients with Addison's disease are inadequate to answer this point, but normal rats treated with Compound A have been shown to have an appreciable decrease in fecal nitrogen.[42]

The greatly increased per cent of uric acid nitrogen during Compound A therapy suggests the breakdown of a tissue high in nucleoprotein. There was no evidence of a marked decrease in circulating lymphocytes in our studies, although this might have been anticipated from the work of Dougherty and White.[43] Studies on tissue cultures suggest that Compound E is much more active in this respect than Compound A.[44] One reason for the small increase in nitrogen excretion which we observed as compared to experimental studies in mice and rats is the relatively larger dosage of Compound A in the animal experiments.[2]

The extent to which gluconeogenesis improves the carbohydrate reserves of experimental animals is still subject to debate.[45,46,47] The maximum increase in urinary nitrogen excretion observed in any one patient during Compound A therapy was 2.8 Gm. daily, and the average for all the experiments amounted to 1.2 Gm. daily. Assuming that 60 per cent of this nitrogen resulted from increased gluconeogenesis, it is clear that under Compound A therapy there could not have been more than 5 to 10 Gm. of carbohydrate formed from protein per day. The failure to observe any significant increase in the fasting blood sugar in patients treated with 30 mg. of Compound A daily is an argument against excessive gluconeogenesis. On the other hand, this dose of hormone was adequate to permit even patients with a severe form of Addison's disease to withstand a twenty-four hour fast. In the case of V. A. there was no indication of increased nitrogen excretion during the early hours of the fast. No appreciable decrease occurred, however, as it progressed and concurrently the blood sugar level was well maintained on Compound A. The normal subject who failed to show an increased nitrogen excretion on therapy showed a marked rise, as compared to the control period, when given intravenous epinephrine in the fasting state. These experiments suggest that increased gluconeogenesis was taking place under an increasing metabolic stress but that the striking improvement in clinical condition might well be due to additional factors influenced by the hormone.

One such factor may be an increased utilization of fat.[48] Another possible effect of Compound A therapy might be a more efficient cellular metabolism and specifically a more active glucose phosphorylating mechanism.[49,50] This is suggested by the increased fall in serum inorganic phosphorus levels observed during intravenous glucose administration under the influence of Compound A as well as Compound F and Lipo-Adrenal Cortex.

One of our cases (J. P.) showed a definite lack of association between an increased nitrogen output and an improved tolerance to a low-carbohydrate diet and fasting while on Compound A therapy. Hypoglycemia no longer occurred. There was no increase, however, in urinary nitrogen during these periods as compared to the control levels without treatment.

The possibility of a carbohydrate-sparing action of Compound A by the direct inhibition of glucose breakdown in the patient with uncomplicated Addison's disease is rather unlikely, since a decreased tolerance to intravenous glucose was observed in only one of three cases under Compound A therapy (K. K.). This patient also failed to show the characteristic rise in blood pyruvate and fall in serum inorganic phosphorus with and without Compound A and would fit best into our diabetic group, twelve of whom showed the same reaction pattern.[51]

It will be recalled that two patients (J. P. and H. J.) showed an absent or diminished renal response to Compound A therapy. Both had had a unilateral nephrectomy previously. Patient J. P. showed a urea

clearance of 50 to 60 per cent, patient H. J. 80 to 90 per cent. Earlier studies had indicated that patients with Addison's disease with only one kidney required relatively higher doses of desoxycorticosterone acetate in order to induce equivalent sodium and chloride retention. Studies on patient J. P. indicated that 5 mg. of desoxycorticosterone acetate daily was followed by a minimal retention of sodium and chloride, certainly much less than that which occurred in other patients treated with the same dose. The findings on Compound A were similar, in that 30 to 45 mg. of Compound A daily failed to induce an increase in the excretion of nitrogen and resulted in only minimal retention of sodium and chloride on three different diets. (Table VIII.) This failure in the usual response occurred also with 6 cc. of Lipo-Adrenal Cortex daily. This rules out any specific deficiency of Compound A. The changes in renal excretion observed in patient H. J. were in the same direction as those observed in the rest of this group, but the magnitude of the change was less. These studies suggest that both the urinary nitrogen and electrolyte effect observed during Compound A therapy are quantitatively related to the total mass of functioning renal tissue which would appear to constitute a limiting factor in this type of response to Compound A therapy.

In the short-term trials of Compound A therapy no increase in the basal blood pressure was noted with doses up to 60 mg. daily. This makes any direct pressor action of the material, such as had been suggested for desoxycorticosterone,[52] appear unlikely. Compound A should thus lend itself to use as a "carbohydrate-regulating" factor in large doses.

SUMMARY AND CONCLUSIONS

1. Fourteen patients with Addison's disease were treated for short periods of time with synthetic 11-dehydrocorticosterone acetate in a total daily dose of 10 to 60 mg. No untoward local or generalized reactions were observed.

2. A decrease in sodium excretion occurred in thirteen of fourteen experiments, and a decrease in chloride excretion was observed in all. The magnitude of the changes in sodium and chloride excretion, however, was much less with Compound A than with desoxycorticosterone acetate therapy, the latter being about twenty times as potent as the former in this respect.

3. In a group of fourteen experiments an increased renal excretion of total nitrogen was observed in twelve, potassium in eleven, and inorganic phosphorus in nine.

4. Uric acid excretion was increased in thirteen out of fourteen experiments. The per cent increase in uric acid nitrogen was approximately twice as great as the increase in total nitrogen. Alpha amino acid nitrogen excretion increased significantly during Compound A therapy in the two experiments in which it was determined.

5. During Compound A therapy fecal fat loss was decreased by 60 per cent in the three patients in whom it was studied, and fecal nitrogen loss was decreased by 37 per cent in one case, with a similar decrease in wet weight.

6. No marked changes occurred in the average values for blood constituents during the short periods of Compound A therapy.

7. Two patients treated with Compound A daily, 30 mg. and 45 mg. respectively, failed to show a significant alteration in intravenous glucose tolerance curve. In one patient 60 mg. of Compound A daily was followed by a distinctly higher glucose tolerance curve. A greater fall in serum inorganic phosphorus was observed in two of three patients during the glucose tolerance test carried out under Compound A therapy.

8. Compound A therapy exerted a consistent effect in preventing hypoglycemic symptoms in patients with Addison's disease

during a prolonged fast or when maintained on a low-carbohydrate, high-protein and high-fat diet.

9. In a normal male subject maintained on a constant diet the administration of Compound A was associated with increased sodium and chloride retention. During a prolonged intravenous glucose-epinephrine test no change in the glucose curve was observed on Compound A therapy. However, there was a significant increase in urinary output of nitrogen, uric acid, potassium, and inorganic phosphorus with a fall in sodium excretion.

10. From metabolic studies it appeared that 15 to 30 mg. of Compound A daily was equivalent in its effect on sodium, chloride and nitrogen excretion to 3 to 6 cc. daily of Lipo-Adrenal Cortex, one-third of the total daily dose of each being given every eight hours.

11. Fifteen mg. of Compound F induced an increase in nitrogen excretion equivalent to that of 30 mg. of Compound A. Compound F, 45 mg. daily, failed to affect the intravenous glucose tolerance curve in the one patient in whom it was studied. Only minimal sodium retention was noted.

12. In most patients Compound A therapy alone in doses of 15 to 30 mg. daily for three to five days failed to effect a significant change in the clinical condition. When this dose of Compound A was added to a basic minimum dose of desoxycorticosterone acetate, 1 to 2.5 mg. daily, a striking improvement over and above that observed with desoxycorticosterone acetate alone was observed.

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Appendix

SUMMARY OF PATIENTS WITH ADDISON'S DISEASE STUDIED IN THIS REPORT

Patient	Age	Sex	Probable Etiology	Duration of Disease	Present Maintenance Therapy	Remarks
J. C.....	49	♂	T.B.	13 years	3 pellets of desoxycorticosterone acetate	From 1933 to 1938 this patient was treated with adrenal extract; from 1938 to present he has been implanted yearly with pellets. Has done well throughout this unusually long period except for crises induced by discontinuing Rx. No striking tendency toward spontaneous hypoglycemic episodes. 17-ketosteroid excretion 2.8 mg. daily. B.M.R. −10 per cent.
J. P.....	27	♂	T.B.	10 years	3 pellets of desoxycorticosterone acetate	Did poorly on treatment (NaCl) from 1936 to 1938. Since 1938 has been treated with yearly implantation of pellets. Tuberculous kidney removed in 1940, and since then he has done well. Crisis when Rx is discontinued and rather marked tendency toward spontaneous hypoglycemic episodes. 17-ketosteroid excretion 2.0 mg. daily. B.M.R. −15 per cent.
E. V.....	48	♂	? T.B.	9 years	4 pellets of desoxycorticosterone acetate	Did poorly from 1937 to 1938 on NaCl and oral adrenal extract; has been remarkably well since Rx with desoxycorticosterone; carries on heavy manual labor; crisis always induced when Rx is discontinued; no striking tendency for spontaneous hypoglycemic attacks at present. 17-ketosteroid excretion 2.0 mg. daily. B.M.R. −6 per cent.
S. B.....	26	♂	Non-T.B.	7 years	3 pellets desoxycorticosterone acetate	From 1939 to 1941 was treated with NaCl, adrenal extract and injections of desoxycorticosterone acetate. From 1941 to present has had pellets implanted each year. Appetite has been finical, and he has had frequent and severe bouts of hypoglycemia. He has done best with supplementary injections of whole adrenal extract. B.M.R. −13 per cent.
N. M.....	43	♂	Non-T.B.	6 years	3 pellets desoxycorticosterone acetate	From 1940 to 1942 this patient was maintained in fair condition on NaCl therapy alone; thereafter he required supplementary hormone therapy; he has been maintained in excellent condition with yearly implantation of pellets; no striking tendency for spontaneous hypoglycemic attacks. Weight loss and weakness develop rapidly if Rx is withdrawn. 17-ketosteroid excretion 4.4 mg. daily. B.M.R. −21 per cent.
M. N.....	45	♀	Non-T.B.	4 years	Percorten 0.2 cc. daily; Upjohn's Lipo-Adrenal Cortex 3 cc. daily; thyroid U.S.P., 60 mg. daily	This patient has been maintained on pellets of desoxycorticosterone acetate. However, there is a striking tendency for edema with more than 2 mg. of hormone daily. Patient has striking tendency for spontaneous bouts of hypoglycemia which are prevented by daily Rx with Upjohn's adrenal extract in oil 3 cc. daily. This latter Rx greatly improves her muscular strength. It has not been possible for her to maintain her weight and strength with 3 cc. daily of Lipo-Adrenal Cortex alone. 17-ketosteroid excretion 0. B.M.R. −18 per cent on thyroid.

SUMMARY OF PATIENTS WITH ADDISON'S DISEASE STUDIED IN THIS REPORT—(*Continued*)

Patient	Age	Sex	Probable Etiology	Duration of Disease	Present Maintenance Therapy	Remarks
H. J.....	55	♂	T.B.	8 years	6 pellets of desoxycorticosterone acetate	From 1939 to 1943 this patient was maintained on large supplementary doses of NaCl (14 gm. daily). In 1940 a right orchidectomy was performed for tuberculosis. In 1943 injections of desoxycorticosterone were begun. A tuberculous kidney was removed in 1944, and since that time he has been maintained on pellets. He has shown a definite tendency to develop hypertension. Hypoglycemic manifestations do not occur except with intercurrent infections. 17-ketosteroid excretion 3.8 mg. daily. B.M.R. −18 per cent.
M. F.....	48	♀	Non-T.B.	3 years	3 pellets of desoxycorticosterone acetate	Addison's disease diagnosed in 1943. Course has been complicated by the development of transitory mild diabetes mellitus and thyrotoxicosis. Recently she had been maintained on thiouracil in addition to pellets of desoxycorticosterone. This patient develops striking muscular weakness which is relieved by treatment with whole adrenal extract. 17-ketosteroid excretion 1.3 mg. daily. B.M.R. +4 per cent.
W. C.....	32	♂	Non-T.B.	13 years	3 pellets of desoxycorticosterone acetate	Addison's disease diagnosed in 1933 at which time patient was treated with a high-sodium low-potassium diet occasionally supplemented by whole extract. Pellets implanted in 1940. Evidence of marked hypothyroidism; ? panhypopituitarism. Occasional bouts of hypoglycemia. On the whole has done well in the last 2 years. 17-ketosteroid excretion 3.6 mg. daily. B.M.R. −30 per cent.
M. T.....	20	♀	Non-T.B.	4 years	3 pellets of desoxycorticosterone acetate	A very severe Addisonian with striking tendency for spontaneous bouts of hypoglycemia. Weight and blood pressure well maintained by pellet therapy. Supplementary whole extract required from time to time during mild infections. 17-ketosteroid excretion 0.2 mg. daily. B.M.R. −18 per cent.
K. K.....	29	♂	Non-T.B.	2 years	3 pellets of desoxycorticosterone acetate	For one year (1944–45) prior to diagnosis o Addison's disease, patient did poorly. Diagnosis established in 1945, and on pellet therapy patient has done very well. No evidence of spontaneous hypoglycemic attacks. 17-ketosteroid excretion 3.2 mg. daily. One undescended testicle and a low B.M.R. −27 per cent suggesting associated thyroid deficiency and a diabetic tendency.
E. H.....	42	♀	Non-T.B.	1 year	3 pellets of desoxycorticosterone acetate	Addisonian of moderate severity complicated by mild thyrotoxicosis. Control of latter has greatly improved adrenal insufficiency. No striking tendency now for hypoglycemic attacks. Has done very well on pellets. 17-ketosteroid excretion 0.6 mg. daily. B.M.R. +4 per cent prior to radioactive iodine therapy.
R. G.....	32	♀	Non-T.B.	6 years	2 pellets of desoxycorticosterone acetate; daily injections of whole adrenal extract.	Panhypopituitarism developed following severe hemorrhage at termination of pregnancy. Evidence of hypothyroidism. Patient develops edema very easily on small doses of desoxycorticosterone and recently has been treated with supplementary injections of whole adrenal extract. Patient experiences many and severe hypoglycemic episodes. 17-ketosteroid excretion 2.6 mg. daily. B.M.R. −35 per cent without thyroid.
V. A.....	37	♀	Non-T.B.	9 months	2 pellets of desoxycorticosterone acetate; daily injections of whole adrenal extract.	Addison's disease developed insidiously over the past year with fatigue as the presenting symptom. Pigmentation has increased since onset. Moderate tendency to spontaneous hypoglycemia. 17-ketosteroid excretion 2.8 mg. daily. B.M.R. −6 per cent

11-Dehydrocorticosterone*

Its Effects on Hypoadrenalism in Man

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DISTURBANCES in water and electrolyte metabolism in adrenal cortical insufficiency are readily controlled by the administration of sodium chloride, desoxycorticosterone or both. These measures in themselves are capable of restoring comparatively good health to a large number of patients suffering from this disorder. Nevertheless, the majority with Addison's disease demonstrate a defect in carbohydrate metabolism as manifested by varying degrees of hypoglycemia. Furthermore, death may occur following the picture of circulatory collapse indistinguishable from the usual crisis except for the absence of electrolyte imbalance or hypoglycemia at the time.

The use of adrenal cortical extracts for the control of disturbances having no apparent association with electrolytes has not proven satisfactory. However, it has been amply demonstrated that certain steroids, notably corticosterone, 17-hydroxycorticosterone, 11-dehydrocorticosterone and 11-dehydro-17-hydroxycorticosterone, have striking effects on protein and carbohydrate metabolism in both normal and adrenalectomized animals. Thorn and his associates[1] have reported improvement in carbohydrate metabolism in patients with Addison's disease after large quantities of 11-dehydro-17-hydroxycorticosterone or corticosterone, while minimal effects were noted following corticosterone in the patient studied by Ferrebee and his co-workers.[2]

The present study was undertaken in order to determine the clinical and metabolic effects of synthetic 11-dehydrocorticosterone* administered to human subjects. Observations were made in three patients, one with hypoadrenalism secondary to hypopituitarism, the other two with uncomplicated Addison's disease.

CASE REPORTS

CASE I. I. R., a thirty-six-year-old, white, male factory worker, was admitted to the Presbyterian Hospital because of general under-development and progressive blindness of the left eye. The diagnosis of a Rathke's pouch tumor was made after the *x*-ray finding of a greatly enlarged sella turcica, together with a hazy shadow of calcium density extending from the anterior sella turcica above and anterior to the chiasm.

On physical examination he was a pale, slow moving male, with thick, dry, cool skin of a waxy-alabaster color, sparse pubic hair, and small genitalia, who appeared less than his stated age. There was blindness of the left eye, right temporal hemianopsia, bilateral optic atrophy and weakness of action of the sixth cranial nerve.

In addition to his physical appearance and *x*-ray findings, the diagnosis of hypopituitarism with secondary hypothyroidism and hypoadrenalism was supported by a markedly reduced basal metabolic rate and serum sodium determinations below normal limits. Death occurred postoperatively a month after this ex-

* Furnished through the courtesy of Merck and Co., Inc., Rahway, N. J.

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periment at which time the diagnosis was established at autopsy and marked atrophy of the pituitary, thyroid and adrenals confirmed.

Experimental. As the patient had been on a regimen of thyroid extract, desoxycorticosterone acetate* (DCA) and added sodium chloride, he was placed in bed for a period of one week on a standard diet without medications before the start of the study. Although food was selected from a diet consisting of an identical weighed menu each day, anorexia led to a small and variable intake. The actual intake of nitrogen and chloride was calculated from the amount ingested daily, the entire daily diet having been previously subjected to direct chemical analysis. Distilled water was used for both drinking and cooking purposes.

Repeated blood pressure determinations were made daily at approximately the same time by not more than two observers using the same arm. The patient was on bed rest throughout the test period. He was weighed each day before breakfast. Fluid balance studies were restricted to careful measurements of fluid intake and urine output.

After a week on the above routine, the patient was started on two control periods (I and II) of four days each. During a third four-day period (III), he received 10 mg. of 11-dehydrocorticosterone acetate (DHCA) intramuscularly twice daily. For a final period of four days (IV), he was placed on 10 mg. of DHCA every six hours.

Intravenous glucose tolerance tests were performed by administering 0.5 Gm. of glucose per kilo of body weight in 200 cc. of distilled water over a thirty-minute period.[1] The respiratory quotients and metabolic rates were carried out under strictly basal conditions and all blood samples were collected under oil before breakfast. The plasma volume was determined with the blue dye T-1824 after thirty minutes in the horizontal position, the optical density being measured with the photoelectric colorimeter,[3] using a sample drawn ten minutes after the injection of the dye.[4] Sodium and potassium determinations were made by direct chemical analysis. Urine sodiums were calculated on aliquots collected daily throughout each period, the result being expressed as average milliequivalents per twenty-four hours. Arginase activity was measured both in terms of packed erythrocytes and of hemoglobin.[5]

Results. No subjective change was noted by this patient following the start of DHCA therapy, and objectively there was also no response. In fact, his course continued downhill, in that his weakness and lassitude increased. His weight remained fairly constant, and the blood pressure persisted at hypotensive levels. (Fig. 1.) His appetite and degree of activity showed no improvement.

DHCA in the dosage employed appeared to have no effect on water metabolism (Table I, Fig. 1) as judged by either the weight curve or the urine output. The plasma volume, originally 30 per cent below the estimated normal for this patient, of 2,624 cc. (based on surface area), fell an additional 5 per cent, and the serum protein and hematocrit values confirmed the absence of significant hemodilution.

Although the diet ingested was unusually small, contained less than 15 milliequivalents of sodium per day, and was sufficiently variable to vitiate proper balance studies, DHCA caused no significant change in chloride balance. The serum sodium and chloride content continued to decrease markedly even during therapy, and sodium output remained in excess of intake. Serum potassium levels were not significantly altered.

Similarly, intravenous glucose tolerance tests before and after DHCA, performed under identical conditions, resulted in practically superimposable curves. A progressive decline in serum urea nitrogen values was apparent even before the use of DHCA, perhaps in association with his poor dietary intake, but the absence of alterations in nitrogen balance and respiratory quotient gave no clue to suggest an increase in gluconeogenesis.

Cholesterol, both free and ester fractions, and plasma vitamin C levels were not materially affected. A single determination of arginase activity after eight days of DHCA therapy showed a rise of more than double the control value. The significance of this change is not clear.

* Furnished through the courtesy of Dr. L. Pirk of Roche-Organon, Inc., Nutley, N. J.

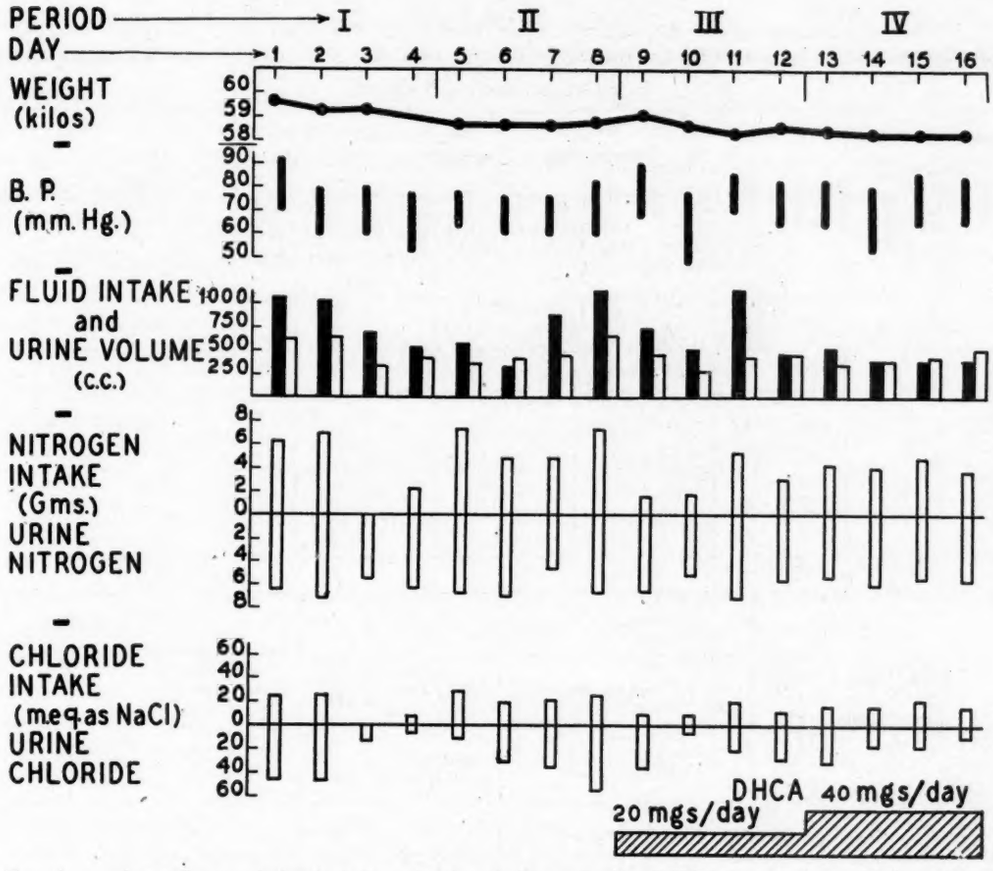

FIG. 1. A, *observations and chemical determinations before and after DHCA in a patient with hypopituitarism.*

Urinary 17-ketosteroid determinations were carried out on aliquots collected daily during each period, the results being corrected in terms of the total output and expressed as average mg. per twenty-four hours. In consideration of the normal daily variation of ketosteroid excretion, no significant change occurred after administration of DHCA. (Table I.)

Three myelocytes and one myeloblast per 100 white cells were observed in a blood smear taken shortly before the end of treatment with DHCA. Abnormal cells had previously not been noted nor did they reappear on subsequent examinations. No striking change took place in the percentage of lymphocytes.

Two weeks after the trial with DHCA and following the restoration of normal serum sodium values by means of saline infusions and DCA, the patient was placed under identical conditions as had been previously employed. He was then given 5 mg. of DCA intramuscularly twice daily for a five-day period. Although slight weight loss was apparent during this phase of study, sodium and chloride levels were maintained and no other significant changes noted.

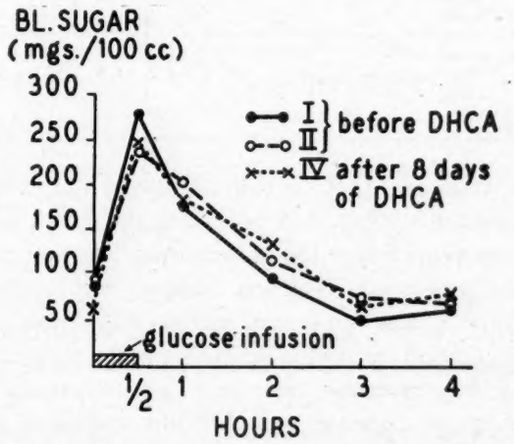

FIG. 1. B, *intravenous glucose tolerance curves before and after DHCA in a patient with hypopituitarism.*

TABLE I

LABORATORY AND CHEMICAL DETERMINATIONS BEFORE AND AFTER DHCA—A PATIENT WITH HYPOPITUITARISM

	Period	Hemoglobin Gm./100 Cc.	RBC, Mill. per Mm.³	WBC per Mm.³	Differential WBC Percentage							Hematocrit, Per Cent Cells	Plasma Volume, C.c.	Serum Proteins Gm.	Alb. /100	Glob. Cc.	Total Circulating Serum Proteins, Gm.
					Polys.	Lym.	Mono.	Eos.	Baso.	Myelocytes	Myeloblasts						
I	No Therapy	11.5	3.9	4775	43	43	10	3	1	0	0	..	....	7.2	5.3	1.9	
II		....	...	6000	60	29	6	3	2	0	0	28	1845	6.7	5.2	1.5	123.6
III	20 mg. DHCA daily	10.2	3.3	4350	59	33	5	1	2	0	0	..	....	6.4	5.2	1.2	
IV	40 mg. DHCA daily	9.8	3.7	7550	61	34	2	2	1	(3)	(1)	27	1705	6.4	4.9	1.5	109.1

	Period	BMR, Per Cent	Respiratory Quotient	Urea Nitrogen, Mg./100 Cc.	Serum				Urine		Cholesterol, Mg./100 Cc.	Cholesterol esters, Mg./100 Cc.	Plasma Vitamin C, Mg./100 Cc.	Arginase		17-Ketosteroids, Mgs./24 hrs. (Av.)
					Sodium	Potassium	Chlorides	CO_2	Sodium	Potassium				U/cc. RBC	U/Gm. Hgb.	
					milliequiv./liter				Milliequiv. per Day (Av.)							
I	No Therapy	−48	.70	21	126.4	4.7	88.7	27.7	26	29	205	142	1.0			1.45
II		−52	.69	13	121.1	4.5	83.3	27.8			199	139	0.9	5.7 ± .5	18.1 ± 1.7	3.18
III	20 mg. DHCA daily	−49	.67	10	116.3	4.2	80.6	25.7			...	...	...	.....	.....	3.25
IV	40 mg. DHCA daily	−46	.71	9	115.2	4.6	77 9	27.3	21	27	182	130	0.9	16.0 ± .2	32.3 ± .3	3.29

CASE II. J. R., a thirty-one-year-old, white, post-office clerk, had been in good health until four years before the present study. At that time he developed weakness, fatigue, hypotension, nausea, skin and buccal mucous membrane pigmentation, as well as several episodes suggestive of hypoglycemic reactions. The diagnosis of Addison's disease was clinically apparent and was established by the finding of repeated serum sodium values which were markedly below normal limits. He was maintained in normal electrolyte and water balance by the subcutaneous administration of 2 mg. of DCA daily as well as by the addition of his regular diet of 4 Gm. of sodium chloride. *X*-ray of the lungs and adrenal areas showed no signs of tuberculosis or abnormal calcification; the erythrocyte sedimentation rate was within normal limits, and repeated urinalyses showed no abnormalities.

Experimental. Throughout the study the patient was satisfactorily maintained on 2 mg. of DCA and 4 Gm. of sodium chloride in addition to that contained in his diet. Before baseline determinations were started, he was observed for a period of two weeks without significant alteration in weight, fluid or electrolyte balance. The conditions of the experiment were the same as those previously described except that the patient was not confined to bed and that a normal appetite permitted a constant dietary intake of identical daily menus (2,200 calories

which included 208 Gm. of carbohydrate and 77 Gm. of protein).

The patient was then started on two four-day control periods (I and II). During a third period of three days (III) and a final period of four days (IV), he received 25 mg. of a sesame oil suspension of DHCA intramuscularly four times daily (every six hours). During the final eighteen hours of drug administration he was given 10 mg. of DHCA acetate intramuscularly every three hours instead of the suspension so that the total dosage on the final day reached 110 mg. It is probable that the daily dose was slightly less than 100 mg. owing to difficulties in complete emptying of the suspended material from ampuls.

Results. No subjective change was noted by this patient following the start of DHCA therapy, and blood pressure readings were unaffected.

DHCA in the dosage employed (100 mg. daily) appeared to have a slight effect on salt and water metabolism (Table II, Fig. 2) in that a small reduction in urine volume and urine chloride content took place in association with an increase in weight of less than one kilo. However, the plasma volume showed little change, nor was there any evidence of hemodilution as judged by serum protein concentration and hematocrit. The serum sodium increased slightly and a decline in sodium output in the urine was noted, but the serum chloride values remained constant throughout the period of treatment. A slight drop in serum potassium was also observed.

Intravenous glucose tolerance tests before and after DHCA, performed under identical conditions, resulted in practically superimposable curves. Nitrogen balance studies and respiratory quotients were unaffected.

TABLE II

LABORATORY AND CHEMICAL DETERMINATIONS BEFORE AND AFTER DHCA—A PATIENT WITH HYPOADRENALISM

Period		WBC, per Mm.³	Differential WBC Percentage					Hematocrit, Per Cent Cells	Plasma Volume, Cc.	Serum Proteins	Alb.	Glob.	Total Circulating Serum Proteins
			Polys.	Lym.	Mono.	Eos.	Baso.			Gm./100 Cc.			Gms.
I		9900	39	41	10	10	..	..	....	6.4	4.4	2.0	
II		10000	28	53	11	8	..	42	2320	6.4	...	...	148.5
III	100 mg. DHCA daily	10200	43	36	10	10	1	..	....	6.4			
IV	100 mg. DHCA daily	11000	47	38	8	6	1	43	2440	6.4	...	...	156.2

Period		BMR, Per Cent	Respiratory Quotient	Urea Nitrogen, Mgs./100 CC	Serum				Urine Sodium, Milliequiv./24 hr. (Av.)	Cholesterol, Mgs./100 Cc.	Arginase		17-Ketosteroids, Mg./24 hr. (Av.)
					Sodium	Potassium	Chlorides	CO_2			U/cc. RBC	U/Gm. Hgb.	
					Milliequiv./liter								
I		−13	.79	13	136.3	4.7	103.1	27.2	87.6	305 350	14.4 ± 0.5	46.5 ± 1.6	6.7
II		−16	.79	14	135.4	4.8	102.2	27.6	79.6	...	15.6 ± 0.1	49.2 ± 0.2	6.1
III	100 mg. DHCA daily	− 9	.79	12	136.3	4.4	103.4	27.7	65.8	274	14.0 ± 0.1	45.4 ± 0.2	30.2
IV		−11	.77	10	138.2	4.0	102.1	25.4	68.2	262	14.5 ± 0.1	46.8 ± 0.3	4.2

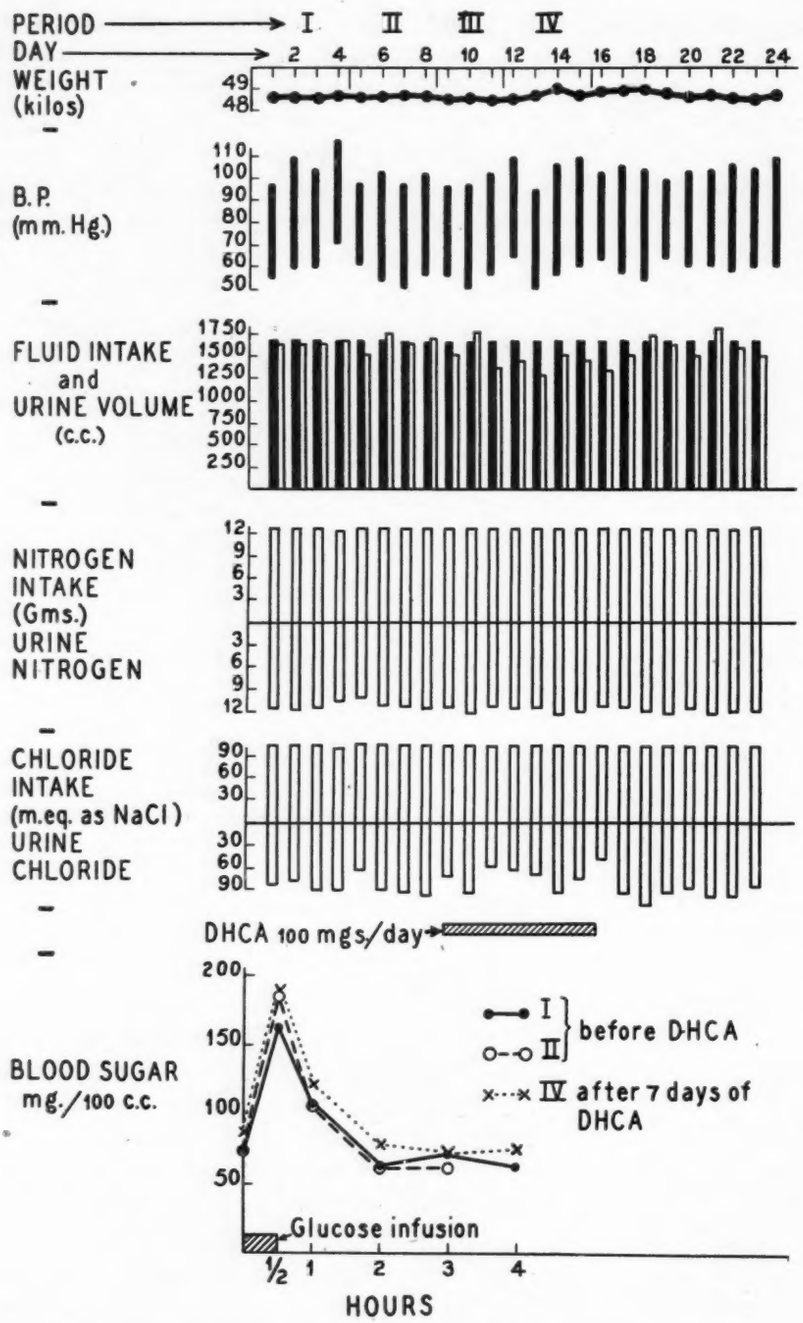

FIG. 2. *Observations and chemical determinations before and after DHCA in a patient with hypoadrenalism.*

Although cholesterol levels fell during DHCA treatment, the lower values were still present a week after therapy. In this patient there was no change in arginase activity.

Urinary 17-ketosteroid determinations showed a marked rise in period III, but this was not sustained.

In association with the administration of DHCA blood counts revealed a fall in the percentage of lymphocytes with a return to higher percentages after the drug was discontinued.

The slight changes noted in salt and water metabolism were only evident while DHCA was being given. The patient was observed under

similar conditions for one week after therapy with a prompt reversal of these trends to original values.

CASE III. A. C., a fifty-two-year-old, Italian embroidery stamper, had been in good health until three years before the present study. At that time he developed weakness, anorexia, nausea, vomiting and skin pigmentation. The diagnosis of Addison's disease was clinically apparent and was established by the repeated finding of serum sodium values which were markedly below normal limits. He was maintained in normal electrolyte and water balance by the subcutaneous administration of 2 mg. of DCA daily as well as by the addition to his regular diet of 6 Gm. of sodium chloride. *X*-ray of the lungs and adrenal areas showed no signs of tuberculosis or abnormal calcification, and repeated urinalyses showed no abnormalities.

The study was carried out several weeks after the incision and drainage of a post-injection thigh abscess. This had been accompanied by moderate adrenal insufficiency and by repeated hypoglycemic episodes (blood sugar 46 mg. per 100 cc.) necessitating oral and occasional parenteral glucose. In spite of 5 mg. of DCA and 5 Gm. of sodium chloride daily, serum sodium values remained below normal.

Experimental. Throughout the study the patient received 5 mg. of DCA and 5 Gms. of sodium chloride in addition to that contained in his diet. The conditions of the experiment were identical with those previously described. He was not confined to bed, and although slight variations occurred in food and fluid intake, the diet was supplied by means of identical weighed daily menus. In order to bring out any effect DHCA might have on gluconeogenesis, a moderately low carbohydrate (100 Gm.) and high protein (100 Gm.) diet was used.

The patient was placed on two control periods of three and four days, respectively (I and II). During a third period of three days (III) and a final period of four days (IV), he received 10 mgs. of DHCA intramuscularly every six hours.

Results. Progressive subjective improvement was noted throughout this experiment but it began before the use of DHCA. Blood pressure readings were variable.

TABLE III

LABORATORY AND CHEMICAL DETERMINATIONS BEFORE AND AFTER DHCA—A PATIENT WITH HYPOADRENALISM

Period		Hemoglobin, Gm.	WBC per Mm.³	Differential WBC Percentage					Serum Proteins,	Urea Nitrogen	Serum				Urine Sodium, Milliequiv./per Day (Av.)
				Polys.	Lym.	Mono.	Eos.	Baso.			Sodium	Potassium	Chlorides	CO_2	
									Gm./100 Cc.	Mg./100 Cc.	Milliequiv./liter				
I		12.1	8,900	42	38	14	6	..	5.7	13	124.2	4.5	91.8	27.0	203
II		11.0	6,950	35	47	9	7	2	5.5	15	126.6	4.5	95.8	26.8	77
III	40 mg. DHCA daily	12.3	7,500	40	41	10	9	..	5.5	13	126.2	4.5	95.8	27.4	73
IV		13.4	8,500	38	39	6	15	2	5.5	16	128.7	4.6	98.7	26.9	100

DHCA in the dosage employed (40 mg. daily) had only doubtful effects on salt and water metabolism (Table III, Fig. 3) in that urine volume was in general reduced and there was a slight increase in weight. A progressive drop in urine chlorides before the use of DHCA made subsequent interpretation difficult. No volume measurements were made but the serum protein concentrations were unaltered. The serum sodium increased in both periods II and IV, and serum chloride values were also rising before DHCA therapy. No change in serum potassium was observed.

DHCA did not prevent reactions suggestive of hypoglycemia (weakness, tremor, slight mental confusion relieved by the oral administration of carbohydrate). One of these occurred

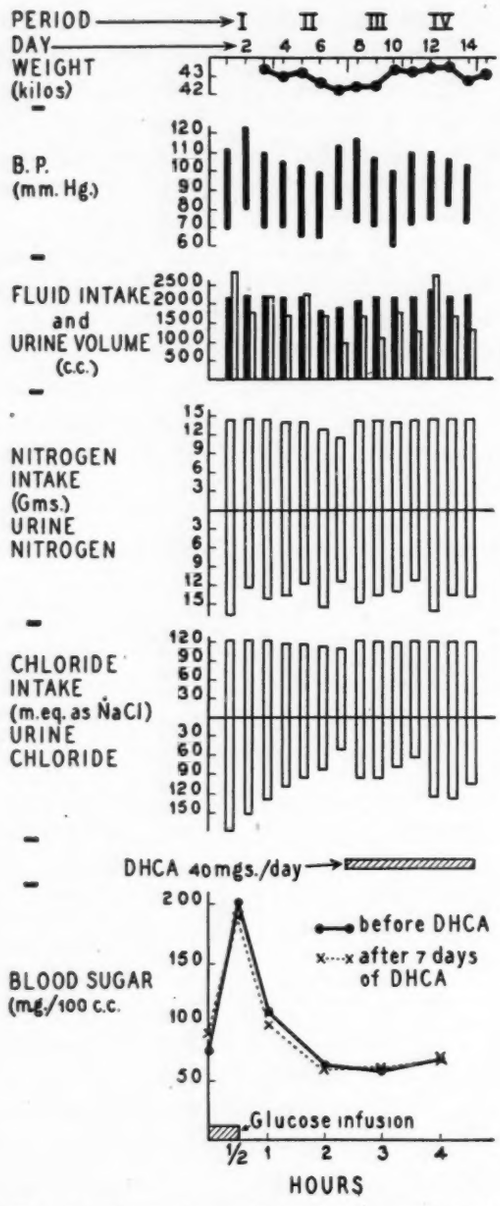

FIG. 3. *Observations and chemical determinations before and after DHCA in a patient with hypoadrenalism.*

three days after the drug had been started and another on the final day. During the latter a blood sugar of 57 mg. per 100 cc. was recorded. Intravenous glucose tolerance tests before and after DHCA resulted in superimposable curves. Nitrogen balance studies showed some daily variation but no significant change after DHCA. The patient was not sufficiently cooperative for respiratory quotient determinations.

The percentage of lymphocytes in the blood smears was unaffected.

SUMMARY AND CONCLUSIONS

1. Metabolic studies were carried out in two patients with Addison's disease and one patient with hypoadrenalism secondary to anterior pituitary insufficiency in order to determine the effects of 11-dehydrocorticosterone (DHCA) administration in doses varying between 20 and 100 mg. daily.

2. DHCA in the higher dosages employed induced slight retention of salt and water; this effect was far less than that induced by much smaller doses of desoxycorticosterone.

3. No effect on carbohydrate metabolism was noted as judged by fasting respiratory quotients or intravenous glucose tolerance curves. Furthermore, the clinical pattern of hypoglycemia, at one time associated with a blood sugar level of 57 mg. per 100 cc., appeared in one patient on several occasions despite the administration of 40 mg. of DHCA daily.

4. No definite or consistent effect of DHCA on nitrogen excretion was observed.

5. DHCA produced no definite effects on basal metabolic rate or serum cholesterol concentration.

6. In one patient, in whom serum albumin and globulin concentrations were followed, no significant change took place after DHCA.

7. The percentage of lymphocytes in the blood smear decreased in one patient while receiving 100 mg. of DHCA daily.

8. Urine 17-ketosteroid excretion was unaffected in one patient receiving 20 and 40 mg. DHCA, but showed a sharp but temporary rise in another following a daily dose of 100 mg.

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Primary Systemic Amyloidosis*

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In its most commonly encountered form, amyloidosis occurs in conjunction with tuberculosis or chronic suppurative lesions. In this type, generally known as secondary amyloidosis, the amyloid deposits are most abundant in the spleen, kidney, liver and adrenal. The earliest deposits occur in and around the walls of capillaries, sinusoids, and, to a lesser extent, small arteries and veins, and the substance is stained in a highly characteristic manner by iodine, Congo red and such metachromatic dyes as methyl violet. In contrast, there is a rare form of diffuse amyloidosis which differs in the following respects: (1) The deposits occur chiefly in skeletal, cardiac and smooth muscle; (2) deposits occur only slightly, if at all, in organs which are the customary site for deposition of secondary amyloid, e.g., liver, spleen, etc.; (3) deposits tend to be nodular rather than diffuse; (4) staining with iodine, Congo red and the metachromatic dyes yields irregular and atypical results; and (5) associated chronic tuberculous or suppurative diseases are lacking. The rarity of the latter, or primary, form of amyloidosis is indicated by the fact that up to 1930 only ten cases had been recorded in the literature. Since then thirty-six additional cases have been reported. From a study of these cases there emerges a fairly definite clinical pattern. This seems not to be generally appreciated, since in only eight of the forty-six cases has a proper diagnosis been made before necropsy. Thus the study of this disorder has been restricted almost entirely to its anatomical features, which are, by now, well established. The two cases which are described below conform to the pattern of those previously recorded in the literature. It is hoped that emphasis of their clinical aspects will help to develop the realization that this disorder can be recognized clinically, and so perhaps lead to a greater opportunity for its study than is afforded by necropsy material alone.

CASE REPORTS

CASE 1. A sixty-four year old white shoemaker was admitted to the Medical Service of the Presbyterian Hospital on April 5, 1944, complaining of swelling of the tongue, face and ankles of three months' duration.

At the age of twenty the patient was told by his doctor that he had tuberculosis and after spending two months in bed was pronounced cured. Since then there have been numerous severe chest colds each winter. One attack of "asthma" is said to have occurred ten years before the present illness, but there had been no recurrences. No other evidence to suggest allergic disease was noted.

The present illness began three months before entry into the hospital, when the patient noted a swelling beneath his chin. At about the same time there appeared swellings of the ankles and legs up to the knees, made worse by standing, and swelling of hands, face and tongue. The enlargement of the tongue rapidly progressed. Within several weeks the tongue was so large that it protruded from the mouth and caused great difficulty in eating and in talking. Concomitantly there occurred a gradual loss in the sense of taste. Shortly before admission bilateral deafness appeared. The patient's hat size had remained constant but his shoe size had recently increased.

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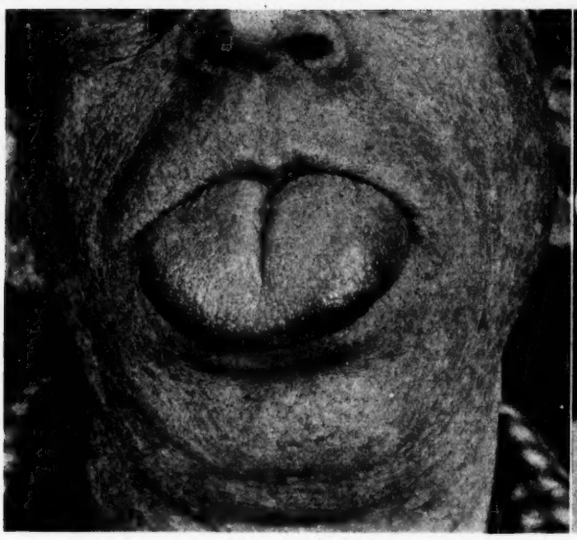

FIG. 1. CASE I. *A sixty-four year old man. The macroglossia produced dysarthria, dysphgia, and even interfered with respiration. Patient ultimately became unable to close his mouth. The submandibular bulge was caused by the pressure of the tongue on the floor of the mouth.*

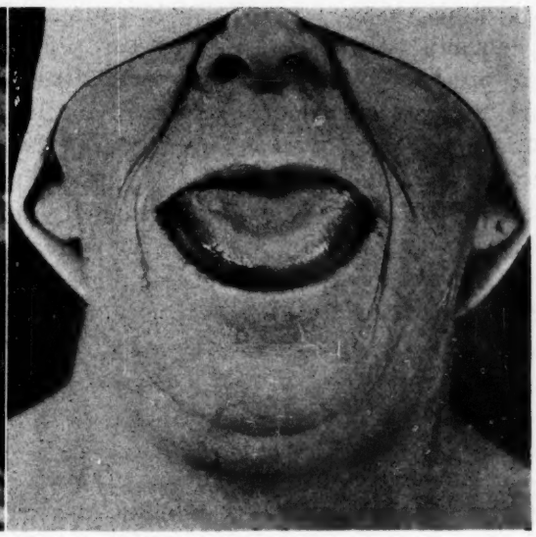

FIG. 2. CASE II. *A seventy-five year old woman. Dysarthria and dysphagia were present. The tongue was symmetrically enlarged, with an impression of upper dentures along its superior margin. Diffuse thickening and induration of the submandibular region was present.*

Physical examination revealed an elderly man with normal temperature, pulse and respiratory rates and a blood pressure of 168 systolic and 110 diastolic. The facies (Fig. 1) was striking because of the prominent and prognathous jaw, the thickened, drooping eyelids and the thickened lips; the lower one was pendulous. The tongue was greatly enlarged, appearing to be at least twice its normal size. Its surface was red but the papillae were normal; on the lateral and inferior margins there were many small but dilated veins. Conspicuous bulging of the submental region was attributed to pressure of the huge tongue on the floor of the mouth. A few moist râles were heard at both lung bases, posteriorly. The heart was slightly enlarged to the left but no murmurs were heard. The liver was firm, smooth and its edge was felt 5 cm. below the right costal margin. The spleen was not palpable. The hands were large, the fingers thick and the palms wide. Moderate ankle edema was present.

The laboratory data were as follows: Hemoglobin, 10 Gm. per cent; red blood cells, 3,220,000 per c. mm.; white blood cells, 9,200 per c. mm. with a normal differential; erythrocyte sedimentation rate, 19 mm. in one hour; Kline test negative; urine, specific gravity 1.025, negative sediment and no albumin or reducing substances; chemical analyses of the blood showed sugar to be 78 to 98 mg. per cent with a normal glucose tolerance curve; cholesterol, 279 mg. per cent. Venous pressure, basal metabolic rate and visual fields were normal. An electrocardiogram showed only low voltage and *x*-ray disclosed a large, boot-shaped heart, tortuous aorta, normal lung fields, slightly enlarged and tufted terminal carpal phalanges, generalized demineralization of the spine and a normal sella turcica. A biopsy of the tongue appeared unremarkable and the patient was discharged to the Vanderbilt Clinic where he received radiotherapy (total 1600 r) to the temporal regions for three months.

Six months later he was admitted to the hospital for the second time because of ankle edema, nocturnal dyspnea and orthopnea which had become progressively worse during the eight weeks preceding readmission. The pertinent facts elicited by physical examination were: blood pressure had fallen to 120 systolic and 78 diastolic; rhonchi were heard throughout both

lung fields; marked pitting ankle and sacral edema and distended neck veins were noted. The tip of the spleen was palpated for the first time and was not tender. Venous pressure had risen to 130 mm. of water and the urine had become abnormal with persistent 4+ albumin, rare hyaline casts, and occasional red and white blood cells. A Congo red test showed only 15 per cent of the dye remaining after one hour. This was interpreted as negative for amyloid. Additional laboratory data included normal inorganic blood phosphate, alkaline phosphatase, urea nitrogen and a negative cephalin flocculation test.

The congestive heart failure was moderately improved by the administration of digitalis and diuretics and the patient was discharged. He was admitted for the third time seven weeks later because of profound weakness, lethargy, anorexia and a weight loss of 11 pounds. The blood urea nitrogen had risen to 63 mg. per cent. The specific gravity of urine ranged from 1.010 to 1.016, albuminuria was persistent (2+ to 4+). The total serum protein was 4.6, the albumin 3.3, and the globulin 1.3 Gm. per cent. Repeated thoracenteses performed for massive bilateral pleural effusions yielded fluid having all the characteristics of a transudate. The patient was afebrile except for an occasional temperature reading of 100°F. Weakness and anorexia were constant and distressing. Congestive heart failure persisted inspite of digitalization and a vigorous dehydration regimen. The patient's condition deteriorated slowly, and he died on the seventy-first day after admission to the hospital, twenty-two months following the initial appearance of symptoms. The final clinical diagnosis was: Acromegaly; hypertensive and arteriosclerotic heart disease; congestive heart failure.

Autopsy examination (No. 14807) was performed fifteen hours after death. The complete anatomical diagnosis follows: Amyloidosis, generalized; hypertrophy of heart; hydrothorax, bilateral; atelectasis, RLL, RUL, LLL; ascites; arteriolarnephrosclerosis, moderate; eosinophilic adenoma of the pituitary; acromegaly; adenoma of adrenal, left; adenomas of thyroid; fibromas of kidneys; polyp of colon; varix of esophageal vein; accessory spleen; arteriosclerosis, generalized; hemorrhage into subdural space, old, organizing; fibrous pleural adhesions; inguinal hernias, bilateral.

Thin, clear yellow fluid was found in the peritoneal cavity (200 cc.) and in the pleural cavities (2,300 cc. right; 700 cc. left). The pleural and peritoneal surfaces were normal, except for fibrous pleural adhesions at the apex of the upper lobe of the left lung. Scattered over the pericardial surfaces were numerous, delicate, grey nodules, ranging in size from pinpoint to pinhead.

The heart was considerably enlarged, weighing 740 Gm. The right auricle was of normal size, but the left was greatly dilated, and the walls of both were thickened, rigid and of the consistency of leather. The capacity of the right ventricle was normal but its wall was slightly thickened. The left ventricle was greatly dilated and its wall was enormously thickened, in places measuring 2.2 cm. The endocardium of the ventricles was not unusual, but in the auricles it was thickened, opaque and over much of its surface was a curious tawny color, which represented, perhaps, antemortem staining of amyloid by Congo red. Both the mitral and tricuspid valves were thickened, especially near their lines of closure. On the auricular aspect of each were many fine, pinhead-sized nodules, some grey, others tawny. These extended from the line of closure up to the valve ring. A few similar nodules were present on the ventricular aspect of the pulmonic valve which, however, was otherwise normal. The endocardial lining of the ventricles and the chordae tendineae were essentially normal. The myocardium throughout presented a most unusual picture. It was extremely firm, waxy and pale. In consistency and in its peculiar friability, it bore a striking resemblance to paraffin. This alteration was diffuse and uniform. The pulmonary and coronary arteries were normal except for slight ateriosclerosis of the latter; this nowhere, however, produced significant luminal narrowing.

The spleen weighed 860 Gm. and it is estimated that 95 per cent of the organ consisted of waxy material which completely obliterated the normal architecture. Lugol's solution, and then dilute sulfuric acid were applied to the cut surface but failed to produce the typical mahog-

any-brown to blue-green color changes. An accessory spleen, about the size and shape of a golf ball, lay at the hilus and appeared to be composed almost exclusively of amyloid.

The liver weighed 2,160 Gm. and although its lobular pattern was normally preserved throughout, it cut with an increased resistancy similar to that experienced with the spleen and the heart.

The kidneys were of normal size (left 140 Gm., right 130 Gm.). The cortical surfaces were diffusely and finely granular, and the cut surface presented the usual changes commonly observed with arteriolarnephrosclerosis. In addition, however, poorly outlined, translucent, waxy areas were noted throughout the parenchyma, especially in the medulla and at the corticomedullary junction.

Remarkable changes were observed throughout the length of the gastrointestinal tract. The tongue was tremendously enlarged, measuring in length 11 cm., in breadth 7.8 cm. and in depth 4 cm. Its superior surface was roughened by coarse papillae. Although it cut with normal resistancy, on the cut surface there appeared between the muscle bundles irregular bands and streaks of translucent, brownish-grey, waxy material. The muscularis of the esophagus, stomach, pylorus and sigmoid colon were conspicuously thickened and the walls were rendered correspondingly rigid. Not only were the muscular layers thickened, but they appeared a curious glassy pale orange-brown. The walls of the remaining parts of the gastrointestinal tract presented similar changes although to a lesser extent.

The pituitary gland was normal in size, but in its anterior lobe there was a poorly outlined, roughly spherical nodule, about 0.4 cm. across which in some areas compressed the surrounding parenchyma. The adrenal glands weighed 8.9 and 9.1 Gm. Their cortices appeared a little broadened. Cortical lipid was abundant. In the left gland there was an adenomatous nodule about 1 cm. across. The thyroid gland weighed 50.9 Gm. and contained numerous nodules, some well encapsulated but others poorly outlined; all appeared to contain the usual amount of colloid.

Urine obtained from the bladder was examined for Bence-Jones protein, but none could be demonstrated.

Histological examination of the heart revealed that the interstitium was enormously increased and was composed largely of amyloid deposits. (Figs. 3, 4.) This material not only caused extensive separation of muscle fibers but encircled many. The more extensively encapsulated fibers were atrophic, appeared greatly compressed, but only rarely did the amyloid extend through the limiting membrane into the sarcoplasm. The presence of varying degrees of fiber atrophy suggested that in the few broad zones which were composed entirely of amyloid, the original fibers had become progressively atrophic and finally disappeared, leaving no vestiges behind. Many of the remaining muscle fibers were pale and vacuolated, but none were necrotic. Nearly all arteries, veins and arterioles had amyloid deposits in their walls. (Fig. 6.) Generally, the vascular amyloid replaced all or nearly all the media; when most extensive it replaced all of the wall from the sub-endothelial layer to the adventitia. These changes were observed in the auricular as well as the ventricular walls and on both the right and left sides of the heart.

Small nodular and more diffuse deposits of amyloid were found in the endocardium, in the tricuspid and mitral valves and in the base of the aortic valve; two minute nodules were also observed in the intima of the aorta just above the internal elastic lamella.

The majority of blood vessels in the lung, especially the medium-sized and small arteries, contained a great deal of amyloid which generally replaced the smooth muscle of the media. The only extravascular amyloid in the lung was observed in portions of the muscularis of a few bronchi. The pulmonary parenchyma contained none of this material.

Sections of the spleen were not readily identifiable, because the pulp had been almost entirely replaced by vast amounts of amyloid. Only a few small clusters of lymphocytes, scattered here and there, remained of the Malpighian bodies. The accessory spleen had an identical appearance.

Amyloid deposits in the liver were of two types: The first was typical of that seen with

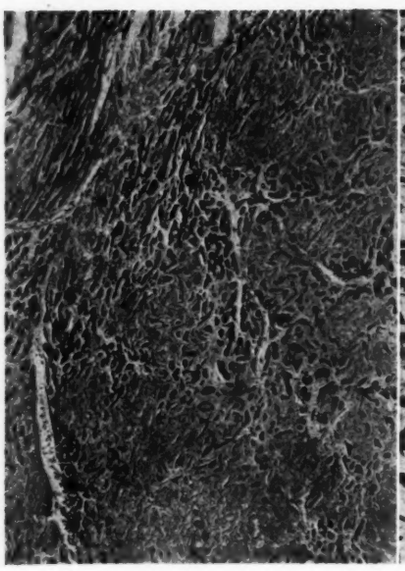

FIG. 3

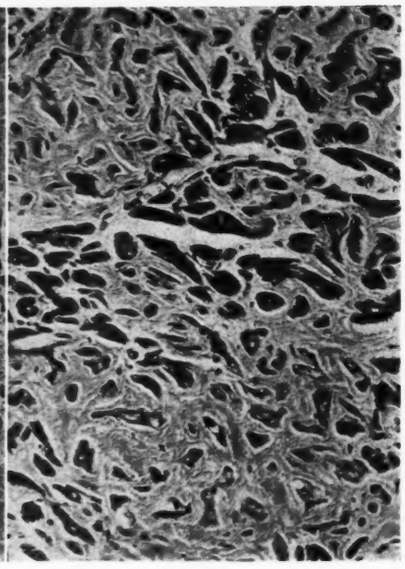

FIG. 4

FIG. 3. *Heart, hematoxylin and eosin stain. The greatly increased interstitium is composed almost exclusively of amyloid.* × 60.

FIG. 4. *Heart, hematoxylin and eosin stain. Amyloid envelopes individual fibers, but only rarely does it penetrate their limiting membrane. Most fibers are atrophic, but they otherwise appear well preserved. A few are vacuolated and pale; none is necrotic.* × 200.

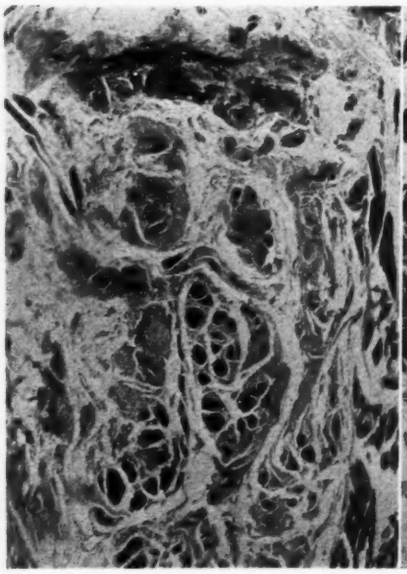

FIG. 5

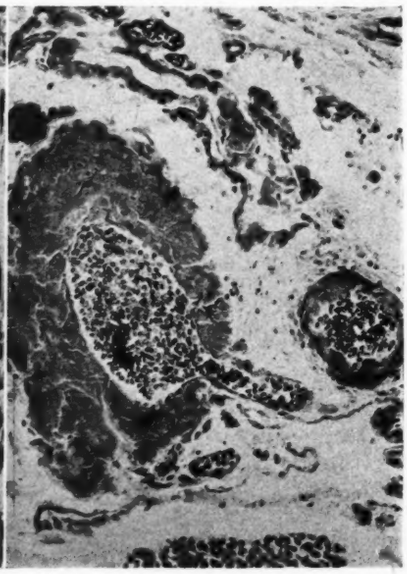

FIG. 6

FIG. 5. *Tongue, hematoxylin and eosin stain. Interstitial deposits of amyloid surround individual fibers. Some muscle fibers are atrophic but most appear well preserved.* × 60.

FIG. 6. *Pancreas, hematoxylin and eosin stain. Smooth muscle of the blood vessel wall has been replaced by amyloid. The vessel is probably a vein, but generally small arteries are most extensively affected. Deposition in the early lesions is limited to the media. There is little or no narrowing of the lumen.* × 200.

secondary amyloidosis, the deposits lying between the sinusoidal endothelium and the hepatic cells causing the latter to become moderately atrophic; in the second type, amyloid occurred in the walls of the blood vessels in the portal areas, in the manner previously described. In the adrenals, amyloid was deposited between sinusoidal endothelium and bands of cortical cells and was most abundant in the reticularis zone. In the periadrenal fatty connective tissue, nearly all blood vessels had extensive amyloid deposits located chiefly in their medias.

The renal deposits occurred chiefly in the glomerular tufts, generally close to the hilus and they occupied anywhere from one-fourth to one-half of many glomeruli. In addition, extensive deposits were observed in arteries, veins and arterioles and in the interstitial tissues of both cortex and medulla. Arteriolar sclerosis was moderately advanced and associated with it were patchy areas of scarring. In the sclerotic small arteries amyloid occurred only in the media, and little, if any, could be identified in the thickened fibrotic intimas. The muscularis of the bladder was extensively replaced by masses of amyloid. The fibromuscular stroma of the prostate also contained irregularly outlined deposits.

A re-examination of the biopsy of the tongue disclosed amyloid only in scanty quantities and confined to the walls of a few small arteries. In the postmortem sections, however, there were extensive deposits in the interstitium related to the skeletal muscle fibers in exactly the same manner that similar formations were applied to cardiac muscle fibers. In addition, vascular and purely interstitial deposits were observed. (Fig. 5.) The extensive amyloid formation appeared great enough to account for the macroglossia. Sections of the esophagus, stomach, small intestine, and colon showed varying degrees of the same changes; amyloid was deposited in the smooth muscle of the muscularis mucosa, the muscular layers, and in the medias of small arteries and less often of arterioles and veins.

Adenomatous nodules enclosed more or less completely by fibrous septa were numerous in the thyroid. In addition, amyloid deposits were present in the walls of blood vessels and appeared as free-lying masses in the interstitium.

In the mesenteric lymph nodes there was atrophy of lymphoid tissue with extensive deposits of amyloid in the interstitium and in the thickened walls of lymphatic channels and small blood vessels. In sections of the diaphragm and rectus abdominus muscles deposits were found closely appressed to sarcolemmal sheaths as in the case of the tongue and heart. Other deposits occurred in the interstitium.

The pancreas, testes, parathyroids and pituitary glands had small amyloid deposits which were confined to the walls of the small blood vessels. (Fig. 6.) No amyloid was found in the brain except in blood vessel walls of the choroid plexus of the lateral ventricle.

The pituitary contained a great number of eosinophiles. In some sections these formed a well defined nodule, but in others they were poorly delimited from the remainder of the anterior lobe.

The tinctorial properties of the amyloid were bizarre: methyl violet produced the most consistent metachromatic staining; the Congo red stain was often suggestive of amyloid but was never unequivocal and often was definitely negative, even in tissues that reacted metachromatically with methyl violet. The reaction to iodine was negative histologically as it had been grossly.

Summary. The patient was an elderly man whose clinical course was characterized by progressive asthenia, congestive heart failure and enlargement of the tongue. Autopsy disclosed widespread amyloidosis involving smooth, skeletal and cardiac muscle, especially that of the tongue, heart and gastrointestinal tract. Although hypertension had been present, it was apparently not severe and it appears much more likely that the congestive heart failure was due to extensive amyloidosis of the myocardium. A complicating feature is the eosinophilic adenoma of the pituitary. This tumor caused mild acromegalic changes which clinically obscured the associated amyloid disease. None of the cases of primary amyloidosis hitherto reported occurred in conjunction with pituitary eosinophilic adenomas, and

we are not aware of the occurrence of amyloidosis in any case of acromegaly. It seems likely, therefore, that the combination of these two relatively rare diseases in this patient is purely fortuitous.

CASE II. A seventy-five year old white widow was admitted to the Presbyterian Hospital on May 3, 1934, because of enlargement of the tongue. Her family and past histories were irrelevant. Fifteen months before entry the patient noticed swelling of her tongue and soreness at its edges. The soreness subsided shortly afterwards, but the swelling persisted for a time and then became progressively greater, resulting, finally, in difficulty in speaking, chewing and swallowing. A weight loss of 15 pounds occurred in the twelve months preceding admission, and during this time *x*-ray treatments were administered to the tongue without benefit at another hospital. A biopsy of the tongue three months before entry revealed only "fibrosis."

On physical examination the patient appeared pale, chronically ill, and slightly cyanotic. The temperature, pulse and respiratory rates were normal and the blood pressure was 120 systolic and 64 diastolic. The tongue was huge, firm, diffusely thickened with tooth impressions along its upper edges. (Fig. 2.) It was not ulcerated. There was fulness of the submandibular region but no generalized lymph node enlargement. Dullness and a few moist râles were present at both lung bases. The heart was enlarged to the left. Occasional extrasystoles and a soft systolic murmur at the apex were noted. Signs of ascites were detected and there was extensive pitting edema of the lower abdominal wall, back and lower extremities.

Examination of the blood yielded the following data: hemoglobin, 80 per cent; red cell count, 3,400,000 per c. mm.; white cell count 5,100 per c. mm. with a normal differential; non-protein nitrogen 28 mg.; cholesterol, 177 mg.; sugar 92 mg.; chlorides 0.61 Gm.; and total proteins 4.9 Gm.; all chemical values referring to the quantity in 100 ml. of blood. The urine contained a trace of albumin, occasional clumps of white blood cells and only rare erythrocytes. The Wassermann reaction was negative. The gastric expression, basal metabolic rate and stool were normal. The electrocardiogram was suggestive of myocardial damage. *X*-ray disclosed: in the chest, increased bronchovascular markings; in the skeleton, mild generalized decalcification; in the descending colon and sigmoid, many diverticula.

The diagnosis remained obscure until a second biopsy of the tongue showed it to be infiltrated by amyloid. The patient was soon discharged but during the ensuing nine months was admitted to the hospital on two additional occasions. The swelling of the tongue was slowly progressive and with it dysarthria and dysphagia worsened. Dyspnea, orthopnea and peripheral edema also became gradually more severe and were usually temporarily improved by digitalis, dehydration and repeated thoracenteses which, incidentally, always yielded fluid of the nature of a simple transudate. The laboratory findings remained essentially unchanged except for the electrocardiograms which showed unequivocal evidence of myocardial damage late in the course. Profound weakness and emaciation, due at least partly to difficulty in eating, increased. Several days before death the patient developed mild erysipelas. She became stuporous but the erysipelas disappeared shortly before exitus, which occurred twenty-four months after the onset of symptoms. The final clinical diagnosis was: Amyloid disease of tongue; arteriosclerotic heart disease; cardiac insufficiency.

Autopsy examination (No. 11,744) was performed eight hours after death by Dr. Homer Kesten. The complete anatomical diagnosis follows: Generalized amyloidosis including tongue, smooth and skeletal muscles, adipose tissue and heart—cause unknown; senile arteriosclerosis—generalized; fibrosis of myocardium; fatty heart; edema of subcutaneous tissues; hydrothorax—bilateral; atelectasis—bilateral; necroses of liver; emaciation; lobular pneumonia; acute cystitis; acute ureteritis—bilateral; acute esophagitis; medial calcification of aorta; Mönckeberg's sclerosis of thyroid artery; diverticula of colon; fibromas of kidney—left; peritoneal adhesions.

Five hundred cc. of thin, clear fluid were found in the left pleural cavity and a slightly greater amount of similar fluid was found in the right. Except for a few fibrous peritoneal ad-

hesions binding the omentum to the anterior abdominal wall, all serous membranes appeared normal. Fat of the subcutaneous tissue and of the epicardium appeared unusually dry and a dark orange.

The heart weighed 240 Gm. All of its chambers were of normal size, and their walls were not thickened. The valves and the chordae tendineae were essentially normal. A small translucent greyish area was noted beneath the endocardium of the right ventricle but otherwise this chamber was normal. In the left ventricle the myocardium appeared pale and was extensively replaced by yellow-grey translucent material which was most marked beneath the endocardium. Coronary arteriosclerosis was moderate but the lumina were everywhere of ample diameter.

The tongue was huge, measuring 9 cm. in length, 5 cm. in maximal width and 4 cm. in its greatest thickness which was near the base. The mucosa was smooth and stained bluish-green. The organ was very firm and on section was found to be composed of pale bands of muscle alternating with stripes of yellowish-grey translucent material. The latter was most pronounced near the base but it did not extend into the muscle of the floor of the mouth or into the submaxillary gland. The submental tissues were not examined. Lymph nodes in this region were not enlarged. In the lower half of the esophagus the muscularis was thick, translucent and grey and a similar change was noted in the muscular layer of the stomach, especially in the pyloric antrum. The serosa of the small intestine was finely granular and opaque. Similar changes were noted in the colon where, in addition, there were many diverticula. The medullas of the adrenals were translucent, firm and conspicuous and the cortices contained an abundance of lipid.

Histologic examination of the tongue presented a most striking appearance. There was a considerable loss of muscle fibers and those remaining were frequently atrophic. These changes were due to an extensive interstitial infiltration by large and small irregularly shaped masses of amyloid. This material never appeared to be intracellular, but occasionally it was observed within the remaining sarcolemmal sheath of an atrophic muscle fiber. Amyloid was present in the form of irregular collars about widely dilated venous and lymphatic vessels, and also was abundant in the walls of arteries. The lumina of many of these vessels were narrowed by a proliferation of loose areolar connective tissue within the intima.

In the inner half of the ventricular myocardium there was extensive muscle fiber atrophy with a corresponding degree of interstitial fibrosis. In this zone, and to a lesser extent in other portions of the section, there were considerable amounts of amyloid. However, these interstitial deposits were not producing evident pressure on muscle cells and the atrophy and the fibrosis were ascribed to conspicuous luminal narrowing of arterioles, small arteries and veins. The extensive, but incomplete, vascular occlusion was due to: first, abundant amyloid in the media and adventitia; and second, and probably of greater significance, thickening of the intima due to considerable proliferation of the subendothelial connective tissue. Occasionally, between the endothelium and the ring of amyloid forming the outer portion of the vessel wall, there were many large foamy phagocytes which contained finely divided fat droplets. An elastic tissue stain demonstrated that the internal elastic lamellae of the most severely involved vessels were to a large extent destroyed. In the large arteries this membrane also was reduplicated. A wide band of amyloid was noted in the deeper portion of the endocardium.

Amyloid deposits were present in many of the alveolar walls, especially about septal capillaries. Practically every pulmonary artery, vein, arteriole and venule had a thickened wall composed of amyloid. The lumina of many of these vessels were greatly narrowed, owing to encroachment upon them by amyloid and by fibrous, thickened intimas. The bronchi contained no deposits.

In the esophagus, stomach and small intestine, similar changes in varying degrees were noted. There was more or less replacement of the muscularis and muscularis mucosa by amyloid, and there were extensive deposits in the walls of blood vessels.

Atrophy of the vaginal musculature and infiltration of this region by amyloid, especially in

the walls of blood vessels and in the immediately surrounding fibrous tissue was a conspicuous feature. Occasionally, foreign body giant cells were observed at the edges of amyloid masses.

Extensive infiltration of the interstitium of the thyroid and parathyroid glands by amyloid and deposits in many of their blood vessels were found. Deposits were quite abundant in skeletal muscle of the floor of the mouth, in intercostal muscle, in the external oblique, transversalis abdominus, rectus abdominus, diaphragm, deltoid, psoas and quadriceps. In these muscles amyloid was closely applied to sarcolemmal sheaths, causing varying degrees of compression and atrophy. The blood vessel walls were extensively involved. In the subcutaneous tissue, in one section, deposits were abundant in the connective tissue between fat cells and in the walls of blood vessels.

In the following organs, amyloid was confined to the walls of blood vessels: aorta, (adventitial vasa vasorum), spleen, liver, pancreas, adrenals, kidneys, submaxillary glands and rib. In the liver, foreign body giant cells surrounded amyloid masses in the portal spaces. Deposits were noted in the fatty connective tissue lying around the pancreas and around the pelvis of the kidney. In the femoral artery the adventitia contained a moderate amount of amyloid.

The staining properties were classical: Amyloid was a brilliant pink with Congo red and was typically metachromatic with methyl violet and iodine green.

Summary. The case was that of an elderly woman whose illness began with swelling of the tongue. The macroglossia gradually led to great difficulty in eating and in speaking. Subsequently the patient developed severe congestive heart failure and profound asthenia. The first biopsy of the tongue was not considered to be of diagnostic value but on the second amyloid deposits were identified. At autopsy widespread amyloidosis was found, affecting chiefly skeletal, cardiac and smooth muscle, especially that of the tongue, voluntary muscles and diaphragm and the gastrointestinal tract. In addition, in practically every organ the blood vessels of all types were involved. In many situations, especially in the heart, vascular narrowing due to amyloid was greatly enhanced by proliferation of fibrous connective tissue. Only in the heart did the luminal narrowing thus produced appear to be of functional significance. In contrast to the preceeding case, but in agreement with the majority of those previously reported, amyloid was absent from the parenchyma of the spleen, liver and adrenals, and from the renal glomeruli.

COMMENTS

There are three major varieties of amyloid disease: (1) Secondary amyloid; (2) primary amyloid, and (3) amyloid associated with multiple myeloma. In all three forms many organs are commonly involved and the process is properly known as diffuse or systemic amyloidosis. In rare instances the deposits are restricted to a single site and occur as tumor-like masses. Such amyloid "tumors" have been observed most often in the upper respiratory tract (nasal septum, larynx, bronchi) and conjunctiva. Nosologically, they may fall into any of the categories listed above.

A formulation of the clinical and morphological features of primary amyloidosis depends, first of all, upon the accumulation for analysis of a sufficient number of cases. This is not simple, since the distinction between the various types of amyloid disease is sometimes vague. For example, in several patients amyloid has been discovered only in the liver, spleen, adrenals and kidneys, yet no chronic suppurative, tuberculous or neoplastic disease was present during life or was discovered at necropsy.[4,7] On the other hand, chronic suppurative bronchiectasis was present in a patient who died with extensive amyloid deposits in the heart and vocal cords.[16] Even in the first of the two present primary cases, amyloid was found in the spleen, liver, adrenals and

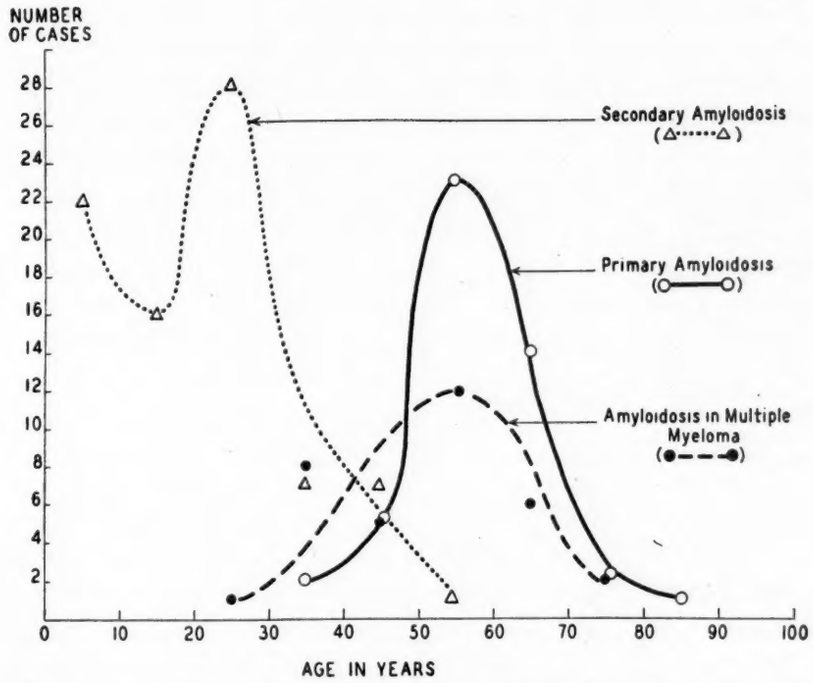

FIG. 7. *Age incidence of the three forms of amyloidosis. The data for amyloidosis complicating multiple myeloma are taken from Atkinson[1] and are based on thirty-seven cases. The data for secondary amyloidosis are based on the eighty-four cases studied by Jacobi and Grayzel.[8] The data of Pearlman[11] agree to the extent that the average age at death of patients with secondary amyloidosis is well below fifty; however, the majority of his* 135 *cases fell in the fourth and fifth decades.*

kidneys in a manner typical of the secondary form. Despite this difficulty, it has been possible to select from the literature forty-six cases of primary amyloidosis. These include the twenty-four summarized by Koletsky and Stecher[37] and the eleven listed by Lindsay and Knorp.[40] To these have been added several more recently recorded cases and the two which are described in the present report, bringing the total number of cases now in the literature to forty-eight.

An analysis of the clinical features of these cases is summarized in Table 1. In age, the patients range from thirty-four to ninety, the average being fifty-six years. (Fig. 7.) The sex division was roughly equal: twenty-six males and twenty-two females constituting the group. Only four of the patients were Negro, the rest were white. The European cases were distributed from the Mediterranean basin to Scandinavia. The most commonly observed signs and symptoms were related to congestive heart failure. Generally, these patients had no evidences of valvular deformities, no hypertension and were in an advanced age group. Consequently, the cardiac diagnosis usually made was arteriosclerotic heart disease. Electrocardiograms were recorded in fifteen cases, and in each was consistent with that diagnosis: low voltage especially of T waves[35, 25, 51, 57] prolonged P-R intervals[25], 2:1 heart block[32], premature ventricular systoles[39], and auricular fibrillation[39] were some of the abnormalities noted. A common interpretation which is recorded is that of "myocardial damage." As in many other progressive forms of heart disease, digitalis was of only temporary benefit.

The peripheral vascular amyloidosis probably did not lead to an increase in peripheral resistance since hypertension is not

a feature of this disorder. On the contrary, the blood pressure levels were generally normal or even low. The few patients who were hypertensive, exhibited a progressive fall in blood pressure with the worsening of their disease (Cases 1, 25, 33). Cardiac enlargement was usually present in cases with congestive failure, and was noted also in some others.[56] Of the largest hearts, namely, those whose weights were 740, 750 and 700 gm., the first two were in patients who had been hypertensive; in the third the blood pressure was not recorded. However, even in the absence of hypertension or valvular disease or advanced coronary arteriosclerosis, heart weights between 500 and 600 gm. were not at all uncommon. Such enlargement can only be attributed to amyloidosis of the myocardium.

TABLE I
INCIDENCE OF SOME SIGNS AND SYMPTOMS IN FORTY-EIGHT CASES OF PRIMARY SYSTEMIC AMYLOIDOSIS

Disturbance	No. of Cases	Per-cent-age
Congestive heart failure	26	54
Dyspnea	23	48
Edema	22	46
Hydrothorax	12	25
Ascites	10	21
Macroglossia	20	42
Dysarthria	16	33
Dysphagia	12	25
Generalized muscle weakness	20	42
Deposits in skin and buccal mucous membranes	19	40
Weight loss	15	31
Pains in extremities	10	21
Abdominal pain	6	13
Lymph node enlargement (localized and generalized)	8	17
Purpura	10	21
Epistaxis	3	6
Hematemesis	3	6
Hematuria (gross)	1	2
Pruritus	2	4
Hypertension (> 140/90)*	8	22
Fever (excluding terminal infection)	0	0
History of allergy	0	0

* Only thirty-six patients had blood pressure readings.

Anatomically, the amyloid occurs diffusely in the interstitium, surrounding and compressing muscle fibers. The latter undergo progressive atrophy. The small arteries, veins and smaller vessels exhibit changes similar to those occurring throughout all other viscera, viz., extensive deposition in the media, leading eventually to replacement of all smooth muscle cells by amyloid. Generally, the process respects the internal elastic lamella, but sometimes the latter membrane is fragmented and ruptured and deposits extend into the intima. Occasionally, proliferation of the subendothelial connective tissue leads to further encroachment upon the lumen. In only two cases, however, was this combination of intimal proliferation and medial amyloidosis sufficiently extensive to have led to myocardial fibrosis (Cases II and 30). In this connection, it ought to be emphasized that although congestive heart failure is common and generally (but inaccurately) attributed to arteriosclerosis, angina pectoris is distinctly rare in the anamneses. (An exception is one of the cases of Dillon and Evans.) Amyloid deposits in the myocardium involve the right as often as the left ventricle, and the auricles quite as frequently as the ventricles. Endocardial and epicardial deposits were often observed (Table II), usually as small nodules but sometimes more diffusely. They appear to be of no functional significance. Valvular deposits were noted in 37 per cent of the cases, but were considered extensive enough to have caused myocardial failure in only two cases: one[38] in which the mitral and tricuspid valves were extensively involved, and another[37] in which the aortic and mitral valves were rigid, stenotic and probably insufficient. Of the instances in which the valves were involved, deposits were observed in the mitral valve six times, in the tricuspid five times, in the aortic and pulmonic valves two times, each; in others the particular valve was not specified.

Enlargement of the tongue is one of the most conspicuous and constant findings. (Figs. 1 and 2 and Tables I, II.) This was so great as to lead to dysarthria and dysphagia on many occasions. The macroglossia is usually symmetrical, and the mucosal papillae remain normally preserved. The swelling is usually not painful, but occasionally (as in Case II) the tongue is tender during the early period of its enlargement. Superficial ulceration of the surface has been noted in several instances (56). In a unique case (32) the lingual amyloid was abundant, but was restricted to nerves and blood vessels and avoided the skeletal muscle. An associated change, frequently observed, is extensive infiltration of the soft tissues and skeletal muscles of the floor of the mouth, submandibular region and cheeks leading to diffuse induration and thickening. The macroglossia has been frequently confused with diffuse carcinoma of the tongue or a lymphangioma. In Case I of the present report it was attributed to the eosinophilic adenoma of the pituitary, which may indeed have contributed to the enlargement.

TABLE II
INCIDENCE OF ORGAN INVOLVEMENT IN FORTY-SIX AUTOPSIED CASES OF PRIMARY SYSTEMIC AMYLOIDOSIS

Organ	Total No. Involved	Percentage	No. with	
			Moderate Parenchymal Deposits	Extensive Parenchymal Deposits
Myocardium	39	85	15	24
Endocardium	28	61	23	5
Valves	17	37	15	2
Pericardium	22	48	19	3
Tongue	26	57	3	23
Stomach	24	52	13	11
Small intestine	22	48	10	12
Colon	20	44	13	7
Esophagus	16	35	8	8
Skeletal muscle	19	41	9	10
Lymph nodes	17	37	7	10
Lungs	17	37	10	7
Kidneys	12	26	7	5
Skin	11	24	4	7
Spleen	11	24	7	4
Adrenals	10	22	10	0
Thyroid	10	22	10	0
Bronchi	9	20	6	3
Aorta	8	17	6	2
Liver	8	17	7	1
Great Veins	7	15	5	2
Bones	5	11	2	3
Joints and tendons	4	9	2	2
Peripheral nerves	3	7	1	2
Gallbladder	2	4	2	0
Pancreas	2	4	2	0
Parathyroid	2	4	2	0
Choroid plexus and meninges	3*	7	0	0
Brain and spinal cord	1*	2	0	0
Pituitary	1*	2	0	0

* An organ which had its only deposits confined to its blood vessels was considered uninvolved. Exceptions are noted by asterisks.* In these amyloid was limited to vascular deposition.

Although it does not cause prominent clinical manifestations, involvement of the gastrointestinal tract is both common and extensive. Unlike secondary amyloidosis in which deposits are found in the mucous membrane, in primary amyloidosis the deposits occur in the smooth muscle of the muscularis, the muscularis mucosa and the blood vessels of the submucosa. In one case, the myenteric plexus was extensively involved. Vague abdominal pain, with cramps and with constipation or with diarrhea[51] are frequent but not conspicuous. Massive hematemesis is recorded in three cases[41, 53, 30] and may be regarded as contributing to death in at least two.[41, 53] In the cases of Steinhaus and of Golden extensive involvement of the prepyloric region of the stomach closely simulated carcinoma. Gastric and intestinal ulcerations were observed in association with extensive bleeding. The amyloid in the blood vessels at the bases of such ulcers was presumed to be a factor in their development. Severe intestinal hemorrhage occurred in two cases.[29, 42]

Deposition of amyloid in skeletal muscles of the extremities and in the diaphragm is frequent (Table III), and associated with it

is a great deal of muscular weakness. The amyloid in this situation is generally found in the interstitium, about muscle fibers, but it rarely penetrates the sarcolemmal sheaths. Blood vessel walls are more or less extensively involved in the extremities but as a rule there is little significant luminal obstruction. In only one case was the vascular amyloid sufficiently occlusive to produce intermittent claudication.[57]

does not seem a very likely one, however, since perivascular hemorrhages are not observed about the involved vessels in other situations. In the few patients in whom the platelets, bleeding and coagulation times and capillary fragility have been studied, these have not been found to be abnormal.

Cutaneous deposits of amyloid were observed in eleven cases. The lesions generally

TABLE III

RESULTS OF SOME COMMONLY PERFORMED LABORATORY PROCEDURES

Test	Average Value	Range	No. of Observations	Remarks
Red blood cell count (millions per c. mm.)	3.9	0.6–6.3	36	Low values in patients with massive gastro-intestinal tract hemorrhage
Hemoglobin (per cent of normal)	74	40–110	35	
White blood cell count (thousands per c. mm.)	8.9	4.8–14.6	33	Normal differentials
Wassermann reaction	All Neg.	.....	32	In 1 patient (46) a past history of two plus. In another (27), history suggestive of lues, but no reaction recorded, see footnote pg. 159
Serum total, protein (Gm. per cent)	5.8	4.6–7.6	9	
Serum albumin (Gm. per cent)	3.3	2.4–4.0	7	
Serum globulin (Gm. per cent)	2.4	1.2–3.6	7	
Congo red test—interpreted as positive (per cent dye disappearing from blood in one hour)	82	60–100	4	
Congo red test—interpreted as negative (per cent dye disappearing from blood in one hour)	42	0–85	5	
Erythrocyte sedimentation rate (mm. in one hour)	30	14–48	6	Cases incompletely summarized.

Hemorrhagic manifestations were frequently observed. Those related to the gastrointestinal tract are noted above and were associated with superficial ulcerations. Epistaxis and bleeding ulcers of skin[40] have been recorded, and in all of these instances it has been implied that amyloidosis of the blood vessels in the bases of the lesions are causally associated. Purpura has been noted on several occasions and was once so extensive as to lead to a mistaken diagnosis of thrombocytopenic purpura.[41] It, too, has been attributed to amyloid involvement of cutaneous blood vessels.[37] This explanation

appear as tense, waxy, yellow, spherical or flat-topped nodules, often simulating a vesicle. In size, they vary from that of a pea to a walnut and are found in the eyelids, the external genitalia, and especially about such mucocutaneous junctions as the lips, anus and nostrils.[36,42] Histologically, the amyloid occurs as nodules, or else more diffusely, in the interstitium and in the blood vessel walls of the dermis and subcutaneous tissue.

Enlargement of lymph nodes has been noted clinically in eight cases and has not been more than moderately conspicuous.

In the autopsy material extensive amyloid deposits have been described in 37 per cent of the cases. The nodal amyloid is distributed throughout the interstitium, and in the walls of blood vessels and lymphatic channels.

Involvement of the lungs is rather frequent in the autopsy material, and as in other situations takes the form of vascular and perivascular deposits with an especial affinity for the media of small arteries. In several instances,[26] extensive deposits were observed in the parenchyma, without an obvious relationship to blood vessels. The bronchial musculature contains less amyloid than smooth muscle elsewhere; in only nine cases were the bronchi involved and never was this very extensive. The lung changes cause no remarkable clinical manifestations. In a few cases[26,50] pulmonary deposits were sufficiently extensive to have caused dyspnea, but in nearly all other patients this symptom seems to have been of cardiac rather than of pulmonary origin.

Although typically the liver, spleen, adrenals and kidneys contain no amyloid, in many cases which are otherwise typical of primary amyloidosis (Cases I, 19 and 25), one or all of these organs contained varying amounts of parenchymal deposits. In one case,[25] the renal amyloidosis led to a nephrotic syndrome. Amyloid deposits were observed in the thyroid in 22 per cent of the cases, but was usually scanty and was never associated with abnormal function. The subject of amyloid goiter recently has been reviewed by Walker[18] who collected from the literature fifty-eight cases, of which forty were part of secondary amyloidosis.

In all other organs, amyloid occurs in varying amounts in the walls of blood vessels, especially the small arteries (Fig. 6). These deposits, however, are of no apparent functional importance. In organs such as the bladder and uterus, the smooth muscle may be replaced by amyloid. Although clinical manifestations such as incontinence or amenorrhea have been attributed in retrospect to these deposits, the clinical-anatomical relationship nearly always remains obscure.

Although blood vessels of the leptomeninges and choroid plexuses occasionally contain amyloid (Cases I and 43), the brain and spinal cord remain singularly free of deposits. An exception in this regard is a case of Goetze and Kruecke,[32] in which extensive deposits were found in blood vessel walls throughout the brain substance. In their case and to a lesser extent in that of deNavasquez and Treble[24] there were also numerous deposits in the peripheral nerves. The latter changes were associated with profound muscular weakness, paralyses, incontinence, impotence, paresthesia and a variety of other neurologic disturbances.

In secondary amyloid and in that produced experimentally, amyloid is characteristically stained a brilliant pink by Congo red and metachromatically by methyl violet (i.e., a rose red in contrast to the purplish blue color of the surrounding tissues). Iodine solution colors secondary amyloid a dark mahogany brown, but has a variable effect on experimentally produced amyloid, especially the earliest deposits. In contrast, the staining properties of primary amyloid are extremely variable. In some cases (Cases II, 25 and 37) the material is colored in the classical manner by Congo red, methyl violet and Lugol's solution. In others, any one or more of the stains produces no distinctive color reaction. In all cases, at least one of these dyes elicited a positive reaction, even if only faintly. Fat stains have demonstrated lipid in the primary amyloid deposits in a few instances.[37]

Some of the recorded laboratory data have been summarized in Table III. Consistent findings are (1) a moderate hypo-

chromic anemia, sometimes becoming very profound if severe gastrointestinal bleeding has occurred, and (2) a moderately elevated erythrocyte sedimentation rate. Of greater interest is the fact that the Congo red test is more often negative than positive and is usually quite equivocal. This is not surprising in view of the diminished postmortem affinity of primary amyloid for this dye. As a diagnostic procedure, therefore, the Congo red test is of greatly limited value in primary as compared with secondary amyloidosis.

Biopsy is the only reliable means for securing a positive diagnosis. In the nine cases in which the disease was recognized before death, the proper diagnosis was provided by a biopsy of the tongue Case II[42, 55, 57], of the skin;[31, 36, 40, 42] of lymph nodes;[25] of a leg muscle;[23] of an ear lobe,[40] and of a tendon.[37] But even in a biopsy amyloid may be overlooked; thus in two of the three biopsies recorded in the present cases, amyloid was not at first recognized because it was present in scanty amounts and because its staining reactions were quite bizarre. It is important, therefore, that the tinctorial variability of this material be recognized and that a variety of stains for amyloid be employed.

Unlike secondary amyloidosis, in which 82 per cent of the patients do not survive more than one year after the onset of symptoms,[11] the duration of primary amyloidosis is relatively long. The average survival after the onset of symptoms was thirty-two months. The longest surviving patient lived fourteen years,[37] and the shortest three months.[33] Death is usually due to congestive heart failure, or to a terminal infection such as pneumonia, erysipelas[58] or septicemia.[39] In a few instances massive gastrointestinal tract bleeding has been contributory.[41]

The pathogenesis of amyloid disease has provoked much thought. Of the many theories which have been elaborated, the one which relates amyloid formation to hyperglobulinemia has been most favored recently.[3,9,10,37] It is well known that hyperimmunized animals and patients with chronic tuberculosis may develop amyloid deposits.[9,11] In these conditions there occur abnormalities of circulating globulins.[3,15] It is less well known that amyloidosis may occur in conjunction with multiple myeloma. Up to 1937, forty such cases were recorded.[1] The resemblance between the amyloid of multiple myeloma and primary amyloid is striking: In their age incidence (Fig. 7), organ incidence (Table IV), and in their staining properties[14] they are much alike. In myeloma, however, hyperglobulinemia is observed in about 50 per cent of the cases, whereas in the cases of primary amyloidosis in whom total serum proteins have been determined, they have been

TABLE IV
COMPARISON OF THE ORGAN INCIDENCES IN THREE TYPES OF DIFFUSE AMYLOIDOSIS

Organ	Percentage of Cases		
	Primary Amyloid	Amyloid Associated with Multiple Myeloma*	Secondary Amyloid†
Heart	85	17	0.9
Tongue	57	17	0.9
Gastrointestinal tract	52	42	4.0
Skeletal muscle	41	21	
Bone and joint	11	29	
Kidney	26	29	72
Spleen	24	21	89
Liver	17	6	63
Adrenal	22	6	41

* Data from Atkinson,[1] 38 cases.

† Data from Rosenblatt,[12] 110 cases. The extent of the gastrointestinal tract involvement is not clearly recorded, but appears nevertheless to be less than is generally believed. Although incomplete in regard to the alimentary tract, Pearlman's data[11] do not differ.

found to be essentially normal. (Table III.)* A possible resolution of this difference is suggested by the fact that when some patients with multiple myeloma develop amyloidosis their serum globulins fall. Thus in one case recently reported[17] the serum globulins were initially 2.5 Gm. per cent. Two and one-half years later, shortly before death, when much amyloid was present, the globulin levels were 0.6, 1.1, and 0.4 Gm. per cent. In another recently recorded case[2] hyperglobulinemia (3.61 Gm. per cent) was present on admission but fell progressively during the last year of life to 1.51 Gm. per cent. In two other cases[2,5] similar sequences were observed. Such serial changes are not seen in the usual case of multiple myeloma, uncomplicated by amyloid, in whom the serum protein pattern remains essentially unaltered.[6] Of the forty cases of myeloma associated with amyloidosis which were collected from the literature by Atkinson,[1] only one had hyperproteinemia.[10] This notation lacks much value, however, because in the great majority of these cases protein determinations were not performed.

Despite the lack of definitive information, it appears that abnormalities in serum globulins may be related to amyloid formation. Such changes have not been demonstrated in the few determinations made on the sera of patients with primary amyloidosis. Further work along this line is plainly indicated. Even if abnormalities of serum globulins should be present, the basis for them is not apparent. In primary amyloidosis there is not only no chronic infection present, but none of the recorded histories is suggestive of an allergic disorder. (Table I.)

*The highest figure, viz., total protein 7.6 with globulin of 3.6 Gm. per cent is recorded in the case of Michelson and Lynch.[12] This case is included as one of primary amyloidosis with great reluctance as it is almost certainly one of multiple myeloma complicated by amyloidosis. In addition to the elevated globulin, the serum calcium was 13 mg. per cent, and Bence-Jones proteinuria was present. *X*-ray examination of the skeleton was negative. Autopsy was not performed.

SUMMARY

Two cases of primary systemic amyloidosis are presented. These bring the total number now in the literature to forty-eight. The disease affects middle aged or elderly individuals, begins insidiously and is slowly progressive. It is characterized chiefly by congestive heart failure, macroglossia, asthenia and weight loss. The Congo red test is often negative and biopsy is the best means for establishing the diagnosis.

The amyloid deposits have atypical staining properties and exhibit a striking affinity for muscle tissue: smooth, striated and cardiac. The heart, tongue, gastrointestinal tract musculature, skeletal muscles and the media of small arteries everywhere are most conspicuously affected.

Amyloid in multiple myeloma and primary amyloid are much alike in organ distribution, age incidence and tinctorial irregularity.

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Relation of Cardiac Enlargement to Hypertension in Acute and Chronic Glomerulonephritis

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In recent years many studies have been reported concerning the cardiac manifestations of acute glomerulonephritis. Cardiac failure as a cause of death in acute glomerulonephritis was first described by Goodhart[1] in 1879, and has been emphasized more recently by Levy,[2] Volhard,[3] Rubin and Rapoport,[4] and Darrow.[5] The incidence of cardiac failure in this disease has been found to be as high as 71 per cent in 138 cases by Whitehill, Longcope, and Williams,[6] 25 per cent in fifty-five cases by Rubin and Rapoport,[4] 20 per cent in 100 cases by Ellis,[7] 16 per cent in 136 cases by Odel and Tinney,[8] and in all of twelve patients with acute glomerulonephritis complicated by edema reported by LaDue.[9] Electrocardiographic changes in patients with acute glomerulonephritis have been discussed by Master, Jaffe and Dack,[10,11] Langendorf and Pick,[12] Williams,[13] and Ash, Rubin, and Rapoport.[14] Cardiac enlargement in this disease has been found to occur in 75 per cent of sixty-seven cases reported by Franke[15] and has been used as evidence of cardiac damage generally in the literature.

The cause of cardiac enlargement and thence cardiac failure in acute glomerulonephritis has been discussed by many authors with varying opinions. Although some[1,2,3,4,9] tend to emphasize the role of hypertension in causing cardiac damage, they also mention additional factors emphasized by other authors[5,6,7,10,11,16,17,18,19] such as generalized arteriolar and capillary damage. It is suggested by the latter group that vascular damage occurs in the heart affecting its structure and function.

An occasional marked lack of correlation between evidence of cardiac damage and elevation of blood pressure in acute glomerulonephritis has been noted in the past. Levy,[2] Odel and Tinney,[8] and Murphy, Grill, and Maxon[20] have each reported a case of this disease with cardiac failure but without significant rise in blood pressure. Whitehill, Longcope and Williams[6] presented an example of acute glomerulonephritis with cardiac enlargement occurring before the onset of hypertension, and also stated that "there is at times no correlation between the degree of hypertension and either the incidence or degree of cardiac failure."

It is the purpose of this paper to emphasize still further the dissociation which may occur between the size of the heart and the degree and persistence of hypertension in glomerulonephritis. Reports follow of (1) three cases of acute glomerulonephritis with persistent enlargement of the heart associated with little or no hypertension, and (2) three cases of chronic glomerulonephritis with persistent hypertension but with little or no increase in heart size above the normal range of cardiothoracic ratio until shortly before death.

CASE REPORTS

CASE I. N. P., a thirty-seven-year old barber, was admitted to the Presbyterian Hospital July 18, 1932, complaining of malaise, feverishness, nausea, slight transient ankle edema and smoky urine of four days' duration, preceded ten days before by a slight sore throat. There was no history of cardiac disease, rheumatic fever or syphilis. One of his children had been treated for acute glomerulonephritis at Babies Hospital. On physical examination, the patient had a temperature of 99.4°F., pulse rate 90, respiratory rate 20, and blood pressure 150/85. The rest of the examination revealed slight bleeding of the gums associated with gingivitis, moderately enlarged tonsils, and slight costovertebral angle tenderness on the right. The heart was normal and there was no edema on admission. Laboratory examination revealed hemoglobin 75 per cent (Sahli), red blood cells 3.7 million, white blood cells 6,250 with 65 per cent polymorphonuclears, lymphocytes 20 per cent, monocytes 11 per cent, eosinophiles 4 per cent. The urine showed a specific gravity of 1.008, acid reaction, albumin 3 plus, and microscopically 30 red blood cells and occasional white blood cells per high power field. No casts were seen. The Wassermann reaction was negative. The sedimentation rate was 72 mm. fall in one hour. Blood urea was .84 Gm. per liter, total serum protein 6.8 per cent. Phthalein excretion was 37 per cent in two hours. A few hemolytic streptococci were cultured from the throat. An electrocardiogram showed no significant findings. A retrograde pyelogram showed a double right kidney pelvis with bifurcation of the ureter. No tubercle bacilli were found in the urinary sediment.

The patient had an uneventful recovery without further rise in blood pressure, and was discharged one month later with a blood pressure of 140/80 and urinary findings of 1 plus albumin and a few red blood cells per high power field microscopically. Two weeks after discharge he was readmitted for tonsillectomy. Immediately after operation there was a sharp increase in urinary findings, with albumin becoming 3 plus and gross hematuria. Blood pressure on this admission varied between 130/85 and 100/55. An *x*-ray examination of the heart at this time showed a total diameter of 15.7 cm. and internal diameter of the chest 27.6 cm., a cardiothoracic ratio of 57 per cent. With subsidence again of his urinary findings, he was discharged two weeks after tonsillectomy.

The patient was followed yearly for thirteen years in the out-patient clinic, and in the follow-up period he had nine more *x*-ray examinations of his heart at least one year apart. The cardiothoracic ratio in that time varied between 55 per cent and 64 per cent despite no rise in blood pressure above 135/85 until the last three years. In 1943, 1944 and 1945 his blood pressure was recorded as 140/90, 160/95 and 170/100, respectively. Urine examinations, usually negative, occasionally showed 1 plus albumin. The patient is now fifty years old. He has never had any symptoms or signs of cardiac damage.

CASE II. J. L., a sixteen-year old high school student, was admitted to the Presbyterian Hospital July 30, 1924, complaining of chills, cough with sputum, chest pain and vomiting for three days. There was no past history of edema, albuminuria, cardiac disease, rheumatic fever or syphilis. On physical examination the temperature was 105.6°F., pulse rate 120, respiratory rate 24 and blood pressure 96/44. There were signs of consolidation over the right middle lobe. The heart had a soft apical systolic murmur, not transmitted, and was thought to be enlarged clinically.

Laboratory examination revealed hemoglobin 95 per cent (Tallquist), red blood cells 5.76 million, white blood cells 24,600 with 89 per cent polymorphonuclears, lymphocytes 11 per cent. The Wassermann reaction was negative. The urine showed a specific gravity of 1.022, acid reaction, albumin 2 plus, and microscopically rare red blood cells per high power field. *X*-ray examination of the lungs showed consolidation in the right middle and lower lobes.

After a briefly stormy course under expectant treatment he was afrebrile in ten days. However, the urinary findings did not clear, and two weeks after admission the urine showed a specific gravity of 1.017, acid reaction, albumin 4 plus, and microscopically was loaded with red blood cells and showed occasional white cells and numerous hyaline and granular casts. The blood pressure during this period varied from

100/65 to 130/90. One week after the sharp increase in urinary findings he developed puffiness about the eyes and pitting edema of the legs. Blood urea was 1.6 Gm. per liter, and phthalein excretion 30 per cent in two hours.

In ten days the edema disappeared, the blood findings were normal, and although examination of his urine showed albumin 2 plus and a few red blood cells per high power field microscopically, he was discharged. No *x*-ray examination of the heart was done on this admission. His blood pressure during his hospital stay had not exceeded 130/100.

One year later he returned to the out-patient clinic for follow-up, and urine examination revealed no abnormalities, nor has it since in eighteen years of yearly visits. His blood pressure in that time has not exceeded 125/85. However, at the first yearly follow-up an *x*-ray examination of the heart showed a total diameter of 15.6 cm. and internal diameter of the chest 28 cm., a cardiothoracic ratio of 56 per cent. During the eighteen years in which he was seen in the out-patient clinic, fourteen *x*-ray examinations were made of the heart, at least a year apart, and the cardiothoracic ratio was seen to vary between 55 per cent and 60 per cent. No symptoms or signs of cardiac damage were ever noted in this time.

CASE III. J. B., a twenty-two year old Scotch caterer, was admitted to the Presbyterian Hospital May 14, 1923, complaining of three weeks of dark urine, frequency, and swelling of the face and legs, preceded two weeks before by a sore throat. There was no history of cardiac disease, rheumatic fever or syphilis. He had had scarlet fever and diphtheria as a child without known residual defects. One sister had had "dropsy" at the age of four.

On physical examination the temperature was 98.6°F., pulse rate 84, respiratory rate 22, and blood pressure 110/70. There was a soft systolic murmur at the apex of his heart, a few fine râles at the base of the right lung, and edema of the face, scrotum and legs. Laboratory examination revealed hemoglobin 103 per cent (Sahli), red blood cells 5.77 million, white blood cells 11,300 with 72 per cent polymorphonuclears, lymphocytes 21 per cent, monocytes 7 per cent. The urine showed a specific gravity of 1.008, acid reaction, albumin 4 plus and microscopically a few red blood cells, occasional white blood cells and many casts. The Wassermann reaction was negative. Blood urea was .32 Gm. per liter. Phthalein excretion was 55 per cent in two hours and fifteen minutes.

The patient recovered uneventfully with disappearance of signs and symptoms in six weeks. While in the hospital his blood pressure varied between 98/60 and 125/68. He was discharged showing 1 plus albuminuria and occasional red blood cells microscopically.

The patient was followed at six-month intervals for the next four years. At the first follow-up visit *x*-ray examination of the heart showed a total diameter of 13.2 cm. and internal diameter of the chest 24 cm., a cardiothoracic ratio of 55 per cent. Five other *x*-ray examinations of the heart were made in the next four years, at least six months apart, in which the cardiothoracic ratio varied from 57 per cent to 58 per cent. During that time urine examination occasionally revealed 1 plus albumin, but no red blood cells were seen microscopically. The blood pressure never rose above 135/85 except on one occasion when it was recorded as 150/95 in one arm and 115/20 in the other. The patient never had symptoms or signs of cardiac damage during the follow-up period. He was later lost to follow-up.

The cases of acute glomerulonephritis presented above had manifestations common to all three of persisting enlarged hearts associated with little or no hypertension. Below are presented three cases of chronic glomerulonephritis with persisting hypertension but with little or no cardiac enlargement clinically until shortly before death.

CASE IV. J. D., a thirteen-year old schoolgirl, was admitted to the Presbyterian Hospital July 26, 1933, complaining of headaches, vomiting and puffy eyelids for eight weeks. Following an attack of scarlet fever, five years before, she had failed to gain weight for two years until tonsillectomy was performed. Three years before admission she had showed 2 plus albuminuria

on one examination. There was no precipitating upper respiratory infection before this admission.

Physical examination showed a temperature of 99.2°F., pulse rate 100, respiratory rate 22 and blood pressure 104/60. Her eyelids were puffy but there was no frank edema. Ophthalmoscopic examination revealed slight haziness on the nasal side of the discs. The heart was normal. There were no other significant findings on physical examination.

Laboratory examination revealed hemoglobin 88 per cent (Sahli), red blood cells 4.4 million, white blood cells 11,500 with 60 per cent polymorphonuclears, lymphocytes 36 per cent, monocytes 4 per cent. The urine showed a specific gravity of 1.015, acid reaction, albumin 4 plus, and microscopically many red blood cells per high power field, and many hyaline and granular casts. The Wassermann reaction was negative. The sedimentation rate was 8 mm. fall in one hour. Blood urea was .29 Gm. per liter, total serum protein 5.4 per cent. Phthalein excretion was 80 per cent in two hours. Throat culture showed hemolytic streptococcus.

Her headaches were thought to be due to "pseudo-uremia," or localized brain edema, and after six weeks she was discharged to be followed in the clinic.

A brief summary of the relationship of the blood pressure and heart size follows:

July 1933—Blood Pressure 104/60–128/60
Oct. 1933—Blood Pressure 120/85–140/100
Nov. 1934—Blood Pressure 122/66–170/110

Total Diameter of heart..... 10.4
Int. Diameter of chest..... 23.9
Cardiothoracic ratio..... 42%

April 1935—Blood Pressure 170/120
May 1935—Blood Pressure 116/68–165/116
Cardiothoracic ratio..... 46%

Oct. 1935—Blood Pressure 178/118
Mar. 1936—Blood Pressure 180/125

Cardiothoracic ratio..... 50%

June 1937—Blood Pressure 180/100

Cardiothoracic ratio..... 45%

Nov. 1937—Blood Pressure 210/130
Oct. 1938—Blood Pressure 200/100
"Heart not enlarged by *x*-ray"

In October, 1938, the patient died in terminal uremia. At autopsy the heart was found to weigh 350 Gm. and was reported as showing mild hypertrophy and little fibrosis with a fibrinous pericarditis. As had been expected, the kidneys showed chronic glomerulonephritis.

Case v. G. C., a twenty-four-year old male clerk, was admitted to the Presbyterian Hospital August 29, 1932, complaining of nocturia, weakness and ankle edema of four years' duration, and known albuminuria for two years. On physical examination the temperature was 100.8°F., pulse rate 92, respiratory rate 24, blood pressure 160/100. There was nothing remarkable about the rest of the physical examination save for puffiness about the eyes and pitting ankle edema.

Laboratory examination revealed hemoglobin 100 per cent (Sahli), red blood cells 5.2 million, white blood cells 12,500 with 70 per cent polymorphonuclears, lymphocytes 20 per cent, monocytes 9 per cent and eosinophiles 1 per cent. The urine showed a specific gravity of 1.005, neutral reaction, albumin 4 plus, and microscopically no red blood cells. The Wassermann reaction was negative. Blood urea was .34 Gm. per liter, total serum protein 4.2 per cent, cholesterol 247 mg. per hundred cc. Phthalein excretion was 70 per cent in two hours. An electrocardiogram showed no important findings. *X*-ray examination of the heart showed total diameter 11.8 cm. and internal diameter of the chest 25.5 cm., a cardiothoracic ratio of 46 per cent.

A brief summary of the relationship of blood pressure to heart size during this admission and subsequently follows:

Sept. 1932—Blood Pressure 115/80–155/110

Cardiothoracic ratio..... 46%

Nov. 1932—Blood Pressure 180/130
Dec. 1932—Blood Pressure 180/110
Aug. 1933—Blood Pressure 160/105

Cardiothoracic ratio..... 45%

Dec. 1933—Blood Pressure 140/90–180/120
Mar. 1934—Blood Pressure 195/130
Dec. 1934—Blood Pressure 205/135

Cardiothoracic ratio..... 49%

June 1935—Blood Pressure 140/95–205/145

Cardiothoracic ratio..... 48.5%

Dec. 1935—Blood Pressure 215/140

Cardiothoracic ratio..... 50%

Sept. 1936—Blood Pressure 225/150
Uremia and death

In September, 1936, the patient died in terminal uremia. At autopsy, nine months after the last *x*-ray examination of the heart, the heart was found to weigh 460 Gm. and was reported as showing moderate hypertrophy and moderate fibrosis of the myocardium. As had been expected, the kidneys showed chronic glomerulonephritis.

CASE VI. D. G., a nineteen-year old male student, was admitted to the Presbyterian Hospital May 14, 1930, with a streptococcic empyema following pneumonia treated at home. Three years before, at another hospital, he had had a tonsillectomy performed for recurrent sore throats, and following the tonsillectomy he had had puffiness of the face for a short time. Since then he had had transient ankle edema twice.

On physical examination the patient had a temperature of 100.8°F., pulse rate 88, respiratory rate 18, and blood pressure 166/110. There was thickening of the radial arteries, physical signs of fluid in the chest, slight clubbing of the fingers, and slight pitting edema of the ankles.

Laboratory examination revealed hemoglobin 50 per cent (Sahli), red blood cells 2.3 million, white blood cells 17,100 with 88 per cent polymorphonuclears, lymphocytes 8 per cent, monocytes 4 per cent. The urine showed a specific gravity of 1.010, neutral reaction, albumin 4 plus and microscopically many red blood cells, many white blood cells, and hyaline and cellular casts. Blood urea was .97 Gm. per liter, total serum protein 4.7 per cent. Phthalein excretion was 35 per cent in two hours.

The patient was operated on twice for his empyema from which he recovered. Although during his hospital stay his edema disappeared, his urine showed no improvement. His blood pressure varied from 130/90 to 168/120.

A brief summary of the subsequent relationship of heart size to blood pressure follows:

May 1930—Blood Pressure 130/90–168/120
July 1930—Blood Pressure 182/110
Oct. 1930—Blood Pressure 210/130
Mar. 1931—Blood Pressure 205/115
May 1931—Blood Pressure 185/120

Total Diameter of heart..... 12.6 Cm.
Int. Diameter of chest..... 26.7 Cm.
Cardiothoracic ratio..... 47%

Dec. 1931—Blood Pressure 200/125

Cardiothoracic ratio..... 47%

Mar. 1932—Blood Pressure 185/120
Dec. 1932—Blood Pressure 220/130

Cardiothoracic ratio..... 51%

In February 1934, one year after the last follow-up visit at the out-patient clinic, the patient was reported to have died at another hospital, presumably of uremia. An autopsy was not obtained.

COMMENT

The three cases of acute glomerulonephritis will be considered first. All of the cases showed the clinical features of acute glomerulonephritis. All of these patients had either a history of edema or had signs of it while hospitalized, and all had albuminuria and hematuria. In addition, two had evidence of nitrogen retention (Cases I and II). Only one case (Case I) had recorded hypertension (150/85) although it is possible, if not probable, that the patient in Case III had an elevated blood pressure that subsided before he entered the hospital three weeks after his initial symptoms.

Although all three patients had no history of rheumatic fever, syphilis, or heart disease, and all had negative Wassermann reactions, *x*-ray examinations of their hearts revealed significant enlargement. Despite the fact that the first *x*-ray examinations of their hearts were made six weeks, one year, and six months after their initial symptoms in Cases I, II and III, respectively, it has been assumed that the cardiac enlargement was due to the acute glomerulonephritis. As mentioned above, cardiac damage is a

frequent concomitant of acute glomerulonephritis. The occurrence of persistent cardiac enlargement in this disease is not widely appreciated. Rubin and Rapoport[4] have reported one case with cardiac enlargement persisting for nine months after the acute attack and Levy[2] has reported one case in which the heart apparently had reënlarged two years later.

Regarding the etiology of the cardiac enlargement in these cases it is difficult to believe that hypertension was a factor of importance. Elevated blood pressure during the attack of glomerulonephritis was recorded in one case only, although, as mentioned above, one other patient had symptoms of glomerulonephritis for three weeks before entering the hospital. The absence of recorded hypertension in two cases and a rise to only 150/85 in the third are good evidence that hypertension was not the cause of cardiac enlargement persisting for many years after acute glomerulonephritis.

The three cases of chronic glomerulonephritis followed the well known pattern of evidence of renal damage followed by hypertension and eventual uremia and death. Two diagnoses were confirmed at autopsy. The first patient (Case IV) had documented hypertension for four years without clinical evidence of cardiac enlargement, and at autopsy showed mild hypertrophy and fibrosis of the myocardium. The second patient (Case V) had known hypertension for three years before his cardiothoracic ratio reached 50 per cent. At autopsy the heart showed moderate hypertrophy and fibrosis. The third patient (Case VI) had documented hypertension for two and a half years before the cardiothoracic ratio became 51 per cent.

Although all three patients with chronic glomerulonephritis showed slight to moderate cardiac enlargement at the end, their hearts had shown no significant clinical enlargement for from eighteen months to four years, despite hypertension during those years. It is possible, of course, that a gradual rise in blood pressure allows the heart to hypertrophy rather than dilate as a reaction to the increased work it must do, and therefore the clinical enlargement is not so striking. As evidence against this hypothesis, the heart in Case IV showed only mild hypertrophy of the myocardium after four years of documented hypertension. One must at least conclude that hypertension associated with chronic glomerulonephritis over a period of years does not necessarily cause enlargement of the heart which can be noted clinically. And the corollary of this is the doubt which is cast upon the theory of hypertension as the etiologic agent of cardiac enlargement in glomerulonephritis.

CONCLUSIONS

1. Cardiac enlargement occurring in acute glomerulonephritis may persist for many years after the acute attack without evidence of significant hypertension at any time.

2. Hypertension occurring in chronic glomerulonephritis may be present for many years without evidence of significant cardiac enlargement as determined clinically.

3. Height of the blood pressure and size of the heart as determined clinically in glomerulonephritis may be completely unrelated.

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Reviews

Bronchogenic Carcinoma*

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AVAILABLE statistical data indicate that there is a progressive increase in the number of deaths annually from bronchogenic carcinoma. While bronchoscopy has aided immeasurably in the diagnosis of carcinoma during life and a correct diagnosis is now being made earlier and more often, this has not kept pace with the advances in surgical treatment. With the remarkable strides made in thoracic surgery, pneumonectomy for carcinoma can now be performed with relative safety and there should be a diminishing number of deaths. In spite of this, however, there still exists a remarkable disproportion between the large number of reported cases of primary carcinoma of the bronchus and the small group of patients that has been successfully treated.[1] Inquiry into this reveals many factors certain of which shall be considered.

If any advance in the surgical treatment of bronchial carcinoma is to be made, it will depend on arriving at a correct diagnosis early in the disease. The diagnostic aids now readily available in addition to a history and physical examination are roentgenology, bronchoscopy, bronchography, sputum study, aspiration biopsy, thoracotomy and most important, *cytologic study of bronchial secretions*. Obviously, demonstration of carcinoma in metastatic lymph nodes, in pleural fluid or by pleural biopsy is only of academic interest. These cases are inoperable and palliative treatment only can be given. The responsibility of diagnosis rests primarily with the clinician who usually is the first to be consulted by the patient; however, the roentgenologist, bronchologist and surgeon must share a part of the burden for they, too, are called upon to aid in the diagnosis. One must agree with Hochberg and Lederer[2] that the future of the treatment of bronchogenic carcinoma is dependent in great measure on its early recognition. The thoracic surgeon has met the challenge and has made greater advances in treatment than has the physician in making an early diagnosis, if one judges from the patients referred to the surgeon.

Overholt's[3] observation, that the average patient sees his physician within three months after the onset of symptoms but does not have a roentgen study of the chest for another three months and that the true diagnosis is not established until nine months after the first doctor saw the patient, is generally shared. Aids in diagnosis are valueless unless they are utilized. The earlier literature on carcinoma was made up largely of advanced cases. Farrell,[4] in 1936, observed that atelectasis of a pulmonary lobe or an entire lung was the most common roentgenographic finding. Pulmonary suppuration was usually observed. There were evidences of extensive involvement with obstruction to large bronchi and the diagnosis then could be made with relatively little difficulty.

Etiology. Many theories concerning the cause of cancer have been presented. Among these are the occurrence of previous bronchopulmonary disease particularly influenza and inhalation of dust,

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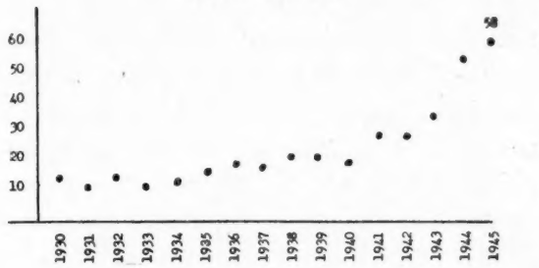
exhaust gases from automobiles and particles of tar from road beds. While these may under certain circumstances be considered as predisposing factors there is too little evidence to warrant their serious consideration. Many writers believe that inhalation of tobacco smoke is a responsible factor. Since chronic irritation is generally accepted as a predisposing cause, there should be ample evidence to support the theory that inhalation of tobacco smoke, particularly from cigarettes, is a factor. This habit is practically universal and a majority of patients with carcinoma of the bronchus smoke either moderately or excessively. Irrespective of its being an etiological factor, smoking more than anything else contributes to delay in diagnosis by masking a common, early and important symptom, namely, cough.

Age and Sex. Carcinoma is an ailment of advancing years, being observed more often between the age of forty and sixty-five years. Although predominately a disease of males, some variations in the collected statistics exist and there is a question whether it may be increasing in females. In a series of fifty consecutive cases diagnosed bronchoscopically and reported in 1933[5] there were forty-eight males and two females (4 per cent). In a number of the series of cases reported from other clinics the percentage of females varied from 12.7 to 21 per cent. In 336 cases observed at the Bronchoscopic Clinic, Jefferson Hospital for a sixteen-year period from 1930 to 1945 inclusive there were 303 males and thirty-three females (10 per cent). (Table 1.)

Symptoms. No group of symptoms or signs can be considered as diagnostic of carcinoma. A multiplicity of effects are apparent when one considers that the disease may involve any part of the bronchial system. While symptoms referable to the respiratory tract are more common, a certain number of cases of carcinoma escape recognition until attention is directed to metastatic deposits in distant organs or structures.

TABLE 1

THIS TABLE SHOWS THE NUMBER OF CASES OF BRONCHOGENIC CARCINOMA OBSERVED ANNUALLY AT THE BRONCHOSCOPIC CLINIC, JEFFERSON HOSPITAL FROM 1930 TO 1945 INCLUSIVE



There is a common mistaken belief that carcinoma always causes symptoms that are referable to the respiratory tract. In 21.7 per cent of sixty cases of bronchial carcinoma studied by Hochberg and Lederer[2] there were no symptoms referable to the chest. Reports on initial symptoms and the frequency of occurrence of symptoms also will vary depending upon the source of the material. In the 336 cases examined at the Bronchoscopic Clinic practically all were referred because of signs or symptoms referable to the air passages and diagnoses of unresolved pneumonia, pulmonary suppuration, pneumonitis, tuberculosis or bronchial obstruction had been made. The symptoms of bronchogenic carcinoma may mimic the symptoms of many other diseases; and unless one is "carcinoma-minded," much valuable time will be spent in needless investigations and treatment. The early symptoms are important as the correct interpretation of these will indicate which studies are necessary to arrive at a prompt diagnosis. This was well stated by Tuttle and Womack[6] who observed that "in the diagnosis of cancer any method that requires metastasis before it can be utilized may as well be discarded

so far as the welfare of the patient is concerned."

Cough without or with sputum is the most common early symptom of carcinoma involving the larger bronchi. It is the result of bronchial irritation, commonly is persistent, frequently fails to respond to the usual methods of treatment and often interferes with sleep. In the presence of the almost universal habit of smoking, cough now is of commonplace occurrence and medical investigation usually is not solicited unless it is aggravated or there are associated symptoms. It appears to be more prominent in carcinoma of the larger bronchi than in peripherally situated lesions.

Sputum in early carcinoma usually is scant and tenacious or may be absent. This becomes more impressive when one attempts to secure a specimen of secretions bronchoscopically for cytologic study. Profuse expectoration is indicative of extensive bronchial infection, the result of bronchial obstruction with retention or breaking down of the growth and formation of an abscess.

Blood-streaked sputum or stippling of mucus with minute reddish spots is an important early sign. It often is observed following severe paroxysms of coughing. Copious hemorrhage usually is a late symptom.

Wheezing respiration is a common symptom of partial obstruction of a bronchus. It is observed early, is influenced by cough and deep breathing and often cannot be demonstrated except during forced expiration. It frequently is not observed by the patient, or being of brief duration, soon is forgotten unless direct inquiry is made. When present it is significant and constitutes strong evidence of partial obstruction to a bronchus.

Pain is not a common, early symptom of cancer originating in a large bronchus. It is, however, considered as a "signal symptom" in a peripherally situated tumor and is due to subpleural or pleural extension. Other symptoms, notably dyspnea, weight loss, weakness, fever and sweats, hoarseness, dyspnea, dysphagia and pleural effusion are evidences of extensive disease and are principally of didactic interest.

Physical signs may be absent or meager in early cancer and are dependent upon the location of the tumor, the degree of bronchial obstruction and retention of secretions. In the peripherally situated lesion physical signs may not be elicited until metastasis occurs. With bronchial obstruction the physical findings may simulate pneumonitis, pneumona, pulmonary suppuration or atelectasis. A diagnosis of pneumonitis later changed to unresolved pneumonia is a common diagnostic sequence.

Diagnostic Aids. Roentgenographic examination is the most valuable diagnostic aid available for discovering the presence of pulmonary disease. Routine roentgen examinations have demonstrated pulmonary disease, either non-specific, tuberculous or neoplastic in the absence of any complaints or physical signs. The greatest difficulty commonly lies in attempting to make a diagnosis on the basis of interpreting a single postero-anterior film of the chest and, a negative opinion having been given, this valuable aid is not utilized again.

As with symptoms, so also there is no classical roentgenologic picture of bronchial carcinoma. Since any portion of the branching bronchial tree may be involved and the effects of bronchial obstruction, retention and infection may alter the clinical picture, misinterpretation of abnormal shadows is not remarkable. An early carcinoma may exhibit only partial bronchial obstruction with obstructive emphysema. This can be recognized only by fluoroscopy or by roentgenograms made at the end of inspiration and expiration. With complete bronchial obstruction of a segmental or lobar bronchus and atelectasis of the corresponding lung, intrabronchial neoplasm should be sus-

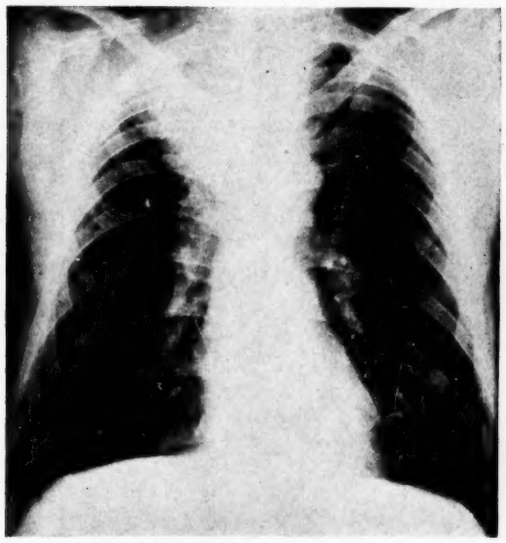


FIG. 1. *Roentgenogram of chest made in case of man, aged fifty-seven years, who gave a history of cough with expectoration of mucoid secretion, occasionally blood tinged for two and one-half months. Recently there had been a numb sensation about the right shoulder girdle. The cough was worse at night and when lying on the right side. On consulting his physician a roentgen study of the chest was made and he was sent to the Jefferson Hospital. On admission he was afebrile. Roentgenogram revealed a dense infiltrating process involving upper lobe of the right lung. The diagnosis was primary bronchogenic carcinoma. Bronchoscopic examination was negative; however, secretions secured from orifice of right upper lobe bronchus revealed cancer cells. A small node found in the right supraclavicular space was removed for study. The diagnosis was metastatic carcinoma. The case was considered inoperable. (Film by Dr. Paul C. Swenson.)*

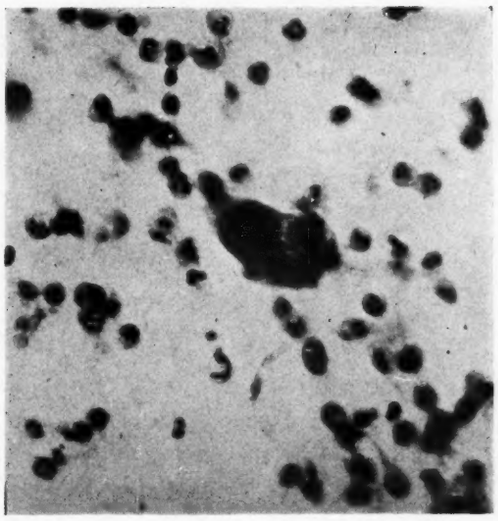


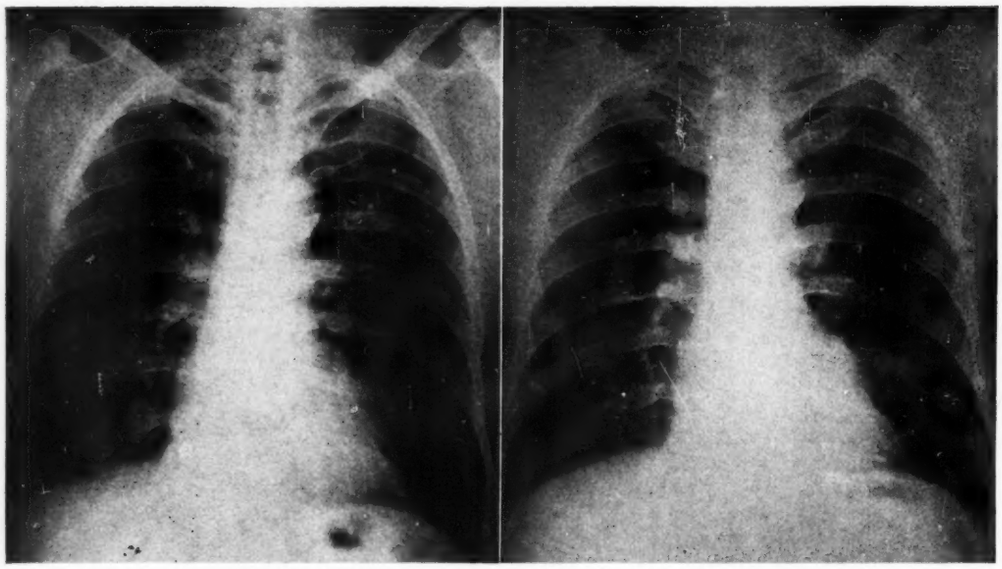
FIG. 2. *Smear of secretions obtained at bronchoscopy in case referred to in Figure* 1 *showing a single large cancer cell in the center of the microphotograph. The borders are fairly sharp and the cytoplasm is bluish-gray and rather dense. The nucleus shows extreme hyperchromatism. There are also present mononuclear phagocytes and neutrophiles. Papanicolaou stain* × 400.

pected. The difficult diagnostic problems are met with in those cases exhibiting roentgen evidences suggesting a small tuberculous or non-specific inflammatory lesion usually peripherally situated and inaccessible bronchoscopically. We are agreed with Bloch and his associates[7] that these present difficulties which cannot be solved with the generally practiced conservative aids.

Bronchoscopy. There is no difficulty in making a positive diagnosis of carcinoma bronchoscopically by biopsy if the growth can be visualized by this means. Too often, however, bronchoscopy is not performed or is utilized late. As a result the number of positive biopsies varies greatly in different clinics; the number of operable cases also varies for the same reason. Holinger and his associates[8] secured positive bronchoscopic biopsies in 136 of 175 cases (78 per cent). In fifty-two cases of pneumonectomy reported by Ochsner[9] and his group, a positive bronchoscopic biopsy was secured in seventeen (32.6 per cent). Since hilar involvement occurs in approximately 70 per cent of tumors, positive bronchoscopic findings should be observed early and bronchoscopy should be utilized in all suspected cases. In peripherally located lesions little help is afforded visually even with a telescopic insert.

Bronchography is of value to demonstrate bronchial obstruction which cannot be visualized bronchoscopically and particularly to visualize the bronchi in an area of suspected pneumonitis shown roentgenographically.

Studies of Sputum. While the results of examination of sputum for cancer cells



A B

FIG. 3. *Roentgenograms made in the case of a man, aged fifty-six years. There was a history of malaise of four weeks' duration, a chill three days before admission followed by hemoptysis of 1 to 2 ounces of blood daily. When admitted the patient was afebrile, the blood pressure was normal, blood studies revealed normal findings and the physical examination was negative for bronchopulmonary disease. Roentgenogram* (A) *revealed an increased density radiating upward from the left hilum into the upper lobe. The findings suggested bronchogenic carcinoma. Sputum studies were negative. At bronchoscopy performed two days later blood tinged secretion was observed coming from the orifice of the left upper lobe bronchus. A specimen removed for cytologic study was negative for cancer. A second bronchoscopy eight days later revealed normal findings. Secretion removed was again negative for cancer cells. A second roentgen study* (B) *made fourteen days after the first examination revealed that the previously observed density had cleared up. A diagnosis of either atypical pneumonitis or pulmonary infarct was made and the patient was discharged. A roentgen checkup made five months after the original study revealed normal findings.*

would appear to give a high percentage of positive diagnoses, this method has met with little success in this country. Our experiences have been disappointing. Since sputum is absent or scanty early and becomes profuse late when suppuration with necrosis supervenes, positive findings, although of much value, are rarely obtained.

Cytologic study of bronchoscopically removed secretions has proven of great value in our experience.[10] The technic of staining and the recognition of cancer cells requires special skill but this also is necessary in all the procedures employed in the diagnosis of bronchopulmonary disease. This method has been carefully checked by studying bronchial secretions secured at postmortem examination or preliminary to bronchoscopic biopsy in known cases of carcinoma. It is now possible to demonstrate cancer cells and even to anticipate the exact histologic diagnosis to be made by bronchoscopic biopsy. In addition by its use a considerable number of positive diagnoses have been made in bronchoscopically inaccessible, peripherally situated lesions which had been diagnosed or suspected as carcinoma by roentgen examination and later corroborated by biopsy, thoracotomy or autopsy. (Fig. 1.) While the series of cases studied is not large, it is our opinion based on these observations that the percentage of positive diagnoses by examination of bronchoscopically removed secretions will exceed that by bronchoscopic biopsy alone. In a series of twenty-five cases of bronchial carcinoma a positive bronchoscopic biopsy was secured in eleven cases and a diagnosis

of carcinoma was made in seven on the basis of deformity, fixity and rigidity observed bronchoscopically. In the remaining seven cases which exhibited no bronchoscopic evidences of carcinoma, cytologic study of bronchoscopically secured secretions revealed cancer cells. (Fig. 2.)

Further studies have shown that considerable dependence can be placed on two or more negative cytologic findings in cases which exhibit suggestive roentgen evidence of bronchial carcinoma. (Fig. 3.)

Aspiration biopsy has its advocates but is condemned by a number of thoracic surgeons. Ochsner[9] and Dolley and Jones have reported cases of implant metastases by this procedure.

Thoracotomy as a diagnostic procedure has a definite place in cases in which carcinoma is strongly suspected but a positive diagnosis cannot be established by the commonly employed procedures.

COMMENT

Bronchogenic carcinoma is one of the common, serious pulmonary diseases occurring between forty and sixty-five years which can be successfully treated if diagnosed early.

There is no classical clinical picture to indicate its presence. The occurrence of cough, without or with sputum which may be blood streaked, wheezing respiration or other discomfort referable to the chest in an adult, particularly a male should suggest cancer as a possibility.

Prompt investigation, including appropriate roentgenologic studies and bronchoscopy with cytologic examination of secretions will establish a diagnosis in a large majority of the cases. Early roentgen findings cannot be conclusive, but in many instances the finding of obstructive emphysema or a shadow in the periphery of a lung before symptoms are manifested is sufficient to warrant further investigation. In the absence of positive findings by the more conservative diagnostic aids, one can always resort to exploratory thoracotomy.

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Experimental and Clinical Evaluation of Synthetic Anti-histaminic Drugs*

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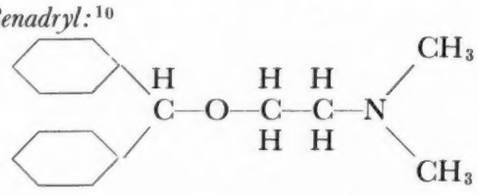
THE increasing evidence that histamine plays an important rôle in anaphylaxis has led to an intensive search for substances which will antagonize the pharmacological effects of histamine in the hope that they will exert a similar action on the allergic reaction in man. Early in the century, Fourneau and his associates in France initiated a search for substances with anti-histaminic properties, but it was not until 1933 that a potent compound was synthesized in the form of 2-isopropyl-5-methylphenoxyethyldiethylamine (929F).[1] In addition to its ability to counteract histamine, it was successful in preventing anaphylactic shock in guinea pigs.[2] Its toxicity was too great, however, to offer any practical application. The search continued, and in 1939 Staub[3] reported that N-phenyl-N-ethyl-N′diethylethylenediamine (1571F) possessed greater anti-histaminic and anti-anaphylactic properties. The problem of toxicity was not solved and related compounds became the subject of further investigation. In 1942, Halpern[4] reported his experiences with two more potent and less toxic compounds, N′phenyl-N′ethyl-N-dimethylethylenediamine (2325 RP), and N′-phenyl-N′-benzyl-N-dimethylethylenediamine (2339 RP). The latter was the more active of the two and its toxicity low enough to warrant clinical trial under the name of antergan. Its use in a variety of allergic disorders has been attended by considerable success according to reports in the French literature.[5] An indication of two purportedly more effective substances has been made recently. N-*p*-methoxybenzyl-N-dimethylaminoethyl α aminopyridine (2786 RP) now being used clinically in France under the name of neo-antergan is allegedly more active and less toxic than antergan.[6] Halpern[7] reports preliminary studies with a new compound (3015 RP), the chemical structure of which has not yet been revealed, possessing eight to ten times the activity of neo-antergan.

Interest in this country has centered around two other compounds, both of which have recently been made available for experimental and clinical trial. Loew and co-workers[8] studied a group of benzhydryl alkamine ethers, and found the most promising member of the group was β-dimethylaminoethyl benzhydryl ether (benadryl). Mayer and his associates[9] reported on the activity of some α-pyridinoethylenediamines of which pyridil-N′-benzyl-N-dimethylethylenediamine (pyribenzamine) was the most active.

PHARMACOLOGY

Benadryl:[10]



It is a white crystalline powder, soluble in water and alcohol, and is stable under ordinary conditions of light and temperature. In addition to its ability to antagonize the

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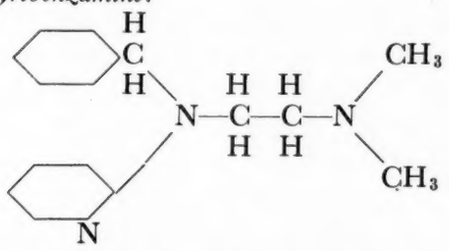
pharmacological effects of histamine, it shows appreciable anti-acetylcholine and anti-barium chloride effect. Lethal doses in animals produce violent excitement, convulsions and death. Chronic toxicity studies in dogs reveal no changes in the blood elements or chemistry over a prolonged period of administration.[11]

Pyribenzamine:



The maximum tolerated subcutaneous dose in guinea pigs is at least 20 mg. per kg. of body weight. The outstanding toxic symptom is excitation to the point of convulsive seizures. It is absorbed readily from the gastrointestinal tract, peritoneal cavity, subcutaneous and intramuscular depots. Its distribution is generalized; nothing is yet known of its destruction, conjugation, deposition or excretion. It shows only slight anti-acetylcholine activity, in contrast to exceedingly high anti-histaminic action. It exerts a very definite local anesthetic action. Chronic toxicity studies in animals, and in a limited number of human subjects, show no blood changes over a long period of administration.

EXPERIMENTAL STUDIES

Histamine Shock. Loew and associates[8] found that benadryl was two to four times more active than 929F and 1571F in preventing fatal bronchoconstriction in guinea pigs from aerosolized histamine solutions. The intravenous injection of benadryl in dogs almost completely abolished the fall in blood pressure produced by small doses of histamine according to Wells et al.[12] Mayer and his co-workers[9] protected guinea pigs from histamine (aerosolized) with as little as 0.1 mg. per kg. of body weight of pyribenzamine. By contrast, 1 mg. per kg. of body weight of antergan (2339 RP) was required for the same protective effect. We[13] compared the protective effect of benadryl and pyribenzamine against intravenous histamine injections in guinea pigs, and found that the anti-histaminic activity of pyribenzamine was approximately six to seven times that of benadryl.

Anaphylactic Shock. Benadryl was reported to have approximately the same protective effect as 1571F against anaphylactic shock in guinea pigs.[14] Wells and associates[15] were able to show significant protection with benadryl against anaphylaxis in dogs. As little as 0.1 mg. per kg. of body weight of pyribenzamine was found by Mayer's group to protect against anaphylactic shock in guinea pigs; while from 1 to 5 mg. per kg. of body weight of antergan was required for the same protection. Despite their difference in anti-histaminic activity, we found benadryl and pyribenzamine equally effective in preventing anaphylactic shock in passively sensitized guinea pigs.[13]

Effect on Skin Whealing Reactions. Thomas Lewis[16] observed that the skin responds to mechanical, thermal, electrical and chemical stimuli by the production of a wheal with surrounding erythema. He further noted that the introduction of specific protein antigen into a sensitized skin site reacted in exactly the same manner. He postulated that all responses of this type were not produced by the stimulus directly, but were the result of the liberation of a diffusible substance from the injured cell, indistinguishable from histamine. We[17] have carried out rather extensive experiments on the effect of benadryl and pyribenzamine on wheals of various origins. The oral administration of either compound reduces the whealing incident to mechanical trauma in dermographic subjects. Oral doses cause a slight impairment in the development of experimentally produced histamine wheals, while the direct local application of these agents

to skin sites, results for a limited time in a reduction of any histamine reaction subsequently produced in that site. This effect may also be obtained by combining the antagonists directly with the histamine solutions. An almost identical action is obtained on wheals produced by testing ragweed sensitive individuals with ragweed extracts (antigen-antibody wheals). Wheals produced by codeine, morphine, atropine, pilocarpine, physostigmine and bee venom are likewise affected by pre-treatment of skin sites with the antagonists. Pyribenzamine shows a slightly greater activity in this respect than benadryl. The similar action on wheals of various origins strengthens Lewis's theory that a common mechanism is responsible for their production (H-substance).

Miscellaneous Actions. Certain possible actions of these drugs have not been thoroughly investigated as yet. One of the more important possibilities to be considered in compounds possessing anti-histaminic activity is their effect in controlling gastric acidity. The earlier French compounds were studied from this point of view and found disappointing.[18] McElin and Horton[19] report the action of benadryl on gastric secretion in man as somewhat inconsistent. In some instances the ability to block the gastric response to histamine was demonstrated. This phase of action deserves further trial. In view of the sedative action of benadryl, we[17] studied the blood pressure following 50 and 100 mg. doses in eight patients. A depressant action was noted which in some cases had not returned to normal at the end of two hours.

THERAPEUTIC APPLICATIONS

Benadryl and pyribenzamine have been administered in a variety of disorders, mostly of an allergic nature. In some ailments the results obtained by various investigators are not in complete accord, while in others the reports are in close agreement. Without question, the effect of these agents is only palliative and symptoms recur in most cases a short time after withdrawal.

Dosage and Tolerance. Considerable variation exists in the individual patient's tolerance to these drugs. In the vast majority, they have been administered by the oral route in the form of 50 mg. tablets or capsules. Smaller amounts (6 to 20 mg. per cc.) have been used for intramuscular and intravenous injection. We have prepared mixtures containing 10 to 25 mg. per drachm for use in infants. The effect of a single dose may become manifest within a very short time and last from two to six hours. In the case of benadryl, 50 mg. three or four times daily was the dose employed in the majority of adults; 10 to 25 mg. doses were used in infants. In our cases approximately 50 per cent experienced some side effects at this dosage, while larger amounts were very poorly tolerated by the majority. Drowsiness, lassitude, vertigo and dryness of the mouth are the most common side effects, and in some instances are severe enough to necessitate discontinuation of treatment. Pyribenzamine seems somewhat better tolerated, and doses of 50 to 100 mg. have been employed four times daily in the majority of our cases.[20] With larger amounts side effects become extremely frequent. We have found that pyribenzamine may produce symptoms of cerebral stimulation (vertigo, nervousness, trembling, insomnia) as frequently as those of drowsiness and lassitude. Both drugs produce anesthetic effects on the oral mucosa when retained in the mouth for more than a short time. While benadryl and pyribenzamine have been administered over a period of months without evidence of serious toxic effects, it is too early to say anything of their hazards from prolonged use.

Urticaria and Angioneurotic Edema. Both drugs seem equally effective in various types of urticarial skin disorders.[17,20,21,22,23] Where more sedation is desirable, benadryl may be more effective; where higher doses are neces-

sary to control symptoms, pyribenzamine is frequently the drug of choice. It has been found possible to afford symptomatic relief to many patients with chronic urticaria to whom other measures have been of little aid. The discomfort of acute urticaria seems likewise benefitted. Needless to say, since these agents are not curative, their use does not obviate the necessity of determining and eliminating the underlying etiology wherever possible. Recently many cases of "serum sickness" reaction characterized by urticarial and angioneurotic lesions with polyarthritis, have been observed following the use of penicillin. The skin lesions are controlled readily by the anti-histaminies, but the joint involvement does not seem to be dramatically affected in the majority of instances. Urticaria from physical agents (heat, cold and light) has likewise responded to this type of medication. The dermographic response of many patients interfering with the diagnosis of allergic sensitivities by skin tests, may be reduced by the prior administration of 50 to 100 mg. of either drug an hour before testing. In a large series of patients, this did not interfere significantly with the whealing reaction to specific allergenic agents.[24]

Dermatitis. Early in the use of these drugs, a marked anti-pruritic effect was noted. In a large number of patients suffering from atopic dermatitis (flexural eczema) there appeared to be no direct effect on the lesions themselves, but the reduction of mechanical trauma incident to scratching resulted in a very definite improvement of the eruption after a few days of treatment.[17,20] A similar anti-pruritic effect was observed in contact dermatitis and various drug eruptions. Benadryl in 1 to 5 per cent solutions has been prepared for local application to inflamed surfaces in a small number of cases. A definite improvement of the dermatitis was observed in only one patient. It is possible that stronger solutions may produce a more beneficial effect.

Allergic Rhinitis, Non-seasonal. The results obtained by various investigators in allergic rhinitis have not been entirely in agreement. We have encountered only a relatively small number of patients who obtained relief with benadryl. In these instances, the effect was most evident in the diminution of rhinorrhea, usually beginning within thirty minutes and lasting for two to six hours. Symptoms invariably recurred on withdrawal. Others[25] report that benadryl is effective in from 28 to 85 per cent of patients treated. We[20] found pyribenzamine to be somewhat more effective in these cases, and observed some degree of symptomatic relief in approximately 40 per cent of those patients treated. Arbesman and associates[23] report improvement with pyribenzamine in 58 per cent of their patients. We attempted the topical use of benadryl in the nose, but were dissuaded from proceeding to any great extent when 0.5 per cent solutions proved too irritating for routine use.

Seasonal Hay Fever. The majority of reports concerning the use of benadryl and pyribenzamine in hay fever have been favorable. Koelsche and associates[26] reported relief in 75 per cent of fifty-two patients treated with benadryl. Others[25] report good results in 59 to 75 per cent of their cases. Friedlaender,[22] on the other hand, employing criteria of daily pollen counts, prevailing atmospheric conditions and control groups was able to attribute improvement to benadryl definitely in but a small percentage of his cases. Doses of 50 to 200 mg. daily were employed in the majority of these studies. The only report on the use of pyribenzamine in hay fever to date has been that of Arbesman's group.[23] They reported that 85 per cent of their patients were benefited. The vagaries of pollen hay fever are such that many unsubstantiated claims have been made in regard to other "cures" in the past. It seems to us that the majority of hay fever reports to date with benadryl and pyribenzamine have not employed the cri-

teria necessary to establish a firm basis for the beneficial effects claimed.

Asthma. The efficacy of the anti-histaminic drugs in asthma in our hands has not been great. We failed to observe results in any of twenty patients treated with benadryl.[17] Koelsche and associates[26] reported four of twelve patients benefited. Friedlaender[22] observed no effect in nine cases of asthma. On the other hand, others[25] report 50 to 65 per cent of asthmatics benefited. We[20] observed two of twenty-five patients with asthma benefited from pyribenzamine. Arbesman and co-workers[23] report that 37 per cent of their patients with non-seasonal asthma and 46 per cent with seasonal asthma helped by pyribenzamine.

Miscellaneous Conditions. Benadryl has been reported to be of benefit in some cases of allergic headache, Ménière's disease and myalgia of the head.[19,27] In three patients with allergic headache treated with pyribenzamine, we noted only one who obtained relief attributable to the drug. Pruritus vulvae in two patients was relieved by either drug. Symptoms invariably recurred within twenty-four hours after the medicine was discontinued.

COMMENT

It is agreed by most investigators that histamine is not the only factor involved in anaphylaxis and allergy. For instance the incoagulability of the blood observed in anaphylactic shock is considered to be due to the release of heparin. No doubt, there are other factors, the identity of which remains obscure. The effect of these anti-histamine substances on both histamine and anaphylactic shock affords additional evidence, however, that histamine may be held accountable for many of the manifestations of anaphylaxis. Their ability to produce symptomatic relief in certain allergic disorders likewise strengthens the rôle of histamine in these phenomena. It is difficult to explain adequately why some allergic symptoms should be better controlled than others. It may be possible that in asthma and rhinitis the histamine release is of an amount too great to be affected by the ordinarily tolerated doses of the antagonist. Perhaps factors other than histamine may account for the differences observed.

The mode of action of this series of compounds is not entirely known. Halpern[4] believes they do not prevent the liberation of histamine or increase its destruction, and is of the opinion that they modify the reaction of the organs in such a way that histamine is incapable of exercising its customary effect. Wells and his associates[15] have shown that benadryl does not prevent the release of histamine during anaphylactic shock in dogs. They believe that the mode of action is most likely a competition between histamine and the drug for a given site of action.[12] From the probable mode of action of these drugs it becomes quite evident that they can act only as palliative agents, and do not eliminate the basic mechanism responsible for allergic disorders. Their use in no way diminishes the importance of a careful search for etiologic factors in order that they may be eliminated where possible, or of measures taken to increase the individual's immunity where removal from the environment is not feasible.

SUMMARY

β-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) and pyridil-N′-benzyl-N-dimethylethylenediamine (pyribenzamine) are two new synthetic substances possessing marked anti-histaminic and anti-anaphylactic properties. They are being used in many allergic disorders with varying degrees of success. Side effects are frequent and varied, limiting the dosage employed. Both drugs appear most successful in controlling the lesions of urticarial dermatoses, and are of value in other conditions in which an anti-pruritic effect is desirable. Their action in allergic rhinitis and seasonal hay

fever is less definite. Beneficial results in asthma are questionable. Where successful, the action of both compounds is of a palliative and not of a curative nature. Their effect is of relatively brief duration, and symptoms almost invariably recur a short time after withdrawal. The importance of determining allergic factors responsible in each case is not diminished by their use.

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Seminar on Antibiotics

A Comparative Study of the Treatment of Tularemia with Immune Serum, Hyperimmune Serum and Streptomycin*

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SINCE 1931 the results of treatment of tularemia with selected agents have been subjected to systematic and periodic study. The agents used were immune serum prepared from horses and goats, hyperimmune serum prepared from these same species and, more recently, streptomycin hydrochloride. Although few patients have received streptomycin, a comparative study at this time may be valuable not only for the relative efficacies disclosed and the establishment of constants for future comparison with an enlarged streptomycin treated series, but also to emphasize the pathological aspects of the disease which impose limitations on the expectations to be realized by all forms of therapy. Failure to understand the nature of the disease processes has led to unwarranted expectations, unrealizable hopes and criticism of therapeutic agents that was founded on unsound premises.

The method of study and the criteria used to assign numerical value to measurable aspects of morbidity have remained unchanged since the effects of immune serum were last reported.[1] This serum was prepared by subcutaneous or by intravenous inoculations of virulent cultures killed with formalin. Hyperimmune serum was prepared by intravenous inoculations of living cultures of maximal virulence.

Comparisons are based on completed records from 832 patients who received immune serum, sixty who received hyperimmune serum, nine who received streptomycin, and 542 who received only symptomatic treatment. Since experience has shown that 125 cases of this clinically variable disease is the minimal number that ensures an acceptable degree of stability the appropriateness of smaller series for comparisons of significance must be demonstrated by their compositions. Since variations in morbidity are caused chiefly by the sequelae of buboes and of visceral lesions, and as variations in mortality are closely related to the frequency of the typhoidal clinical type, the compositions shown in Table 1 indicate that all groups are suitably comparable. Even so, morbidity and mortality data from the two small series may be expected to be less reliable than those from the large groups. Excess variation of morbidity data would be expected, if only because of the differences between the days of disease upon which these patients were treated, from the third to the one-hundred-third days for the nine patients treated with streptomycin. A fairer way to appraise the value of differences between small series of a variable disease in which the time of administration of therapy is important is to

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compare the respective therapy-to-recovery intervals, the time required to effect recovery after therapy was administered. Since an outstanding feature of the response to streptomycin is its uniformity in time of appearance and progressiveness, it is probable that the therapy-to-recovery intervals already observed will not be changed greatly by subsequent experience.[2] Therefore, although morbidity and mortality data will be presented for the groups treated with hyperimmune serum and streptomycin, greater emphasis will be placed on the comparisons of therapy-to-recovery intervals.

TABLE I
THE INCIDENCE OF THE CLINICAL TYPES AND OF PNEUMONIA IN THE COMPARED GROUPS

Clinical Types	No. of Cases	Frequency Per Cent	No. with Pneumonia	Pneumonia Frequency Per Cent
Immune Serum				
Ulceroglandular	722	86.7	107	14.8
Oculoglandular	23	2.8	3	13.0
Glandular	21	2.5	2	9.5
Typhoidal	66	7.9	34	50.7
Total	832	....	146	17.5
Hyperimmune Serum				
Ulceroglandular	48	80.0	7	14.6
Oculoglandular	1	1.7	0	0
Glandular	2	3.3	1	50.0
Typhoidal	9	15.0	9	100.0
Total	60	....	17	28.8
Streptomycin				
Ulceroglandular	8	88.9	1	12.5
Oculoglandular	0	0	0	0
Glandular	0	0	0	0
Typhoidal	1	11.1	1	100.0
Total	9	....	2	22.2
Untreated				
Ulceroglandular	437	80.6	58	13.3
Oculoglandular	32	5.9	0	0
Glandular	12	2.2	1	8.3
Typhoidal	61	11.3	27	44.3
Total	542	....	86	15.9

Comparison by Individual Cases. Two records were selected for a comparison by individual patients, one treated with immune serum, the other with streptomycin. Both men were treated on the wards of the Cincinnati General Hospital, service of Dr. M. A. Blankenhorn. Each had the ulceroglandular clinical type with tularemic pneumonia, and each received therapy at about the same stage of disease. The first patient was selected for the additional reason that serum sickness did not seriously complicate the temperature curve.

CASE I. W. H., a laborer, aged thirty-three, hunted wild rabbits on November 24th. The onset occurred on December 1st., with pain across the lower back, headache, fever, chills, drenching sweats and prostration. He was bedridden from the onset. On the third day of disease a small painful lump appeared in the right axilla, followed in two days by a 6 mm. papule on the dorsum of the right index finger which ulcerated on the seventh day. He became progressively weaker, developed a harassing cough productive of scanty, colorless sputum on the ninth day and became dyspneic while lying quietly in bed.

He was admitted on the fifteenth day of disease with unabated general symptoms and worsened respiratory symptoms, including pain in the right thorax and moderate cyanosis. The significant findings were temperature from 102° to 104°F., physical signs and *x*-ray evidence of an extensive area of pneumonia in the upper right lobe, a bubo measuring 2 cm. in diameter in the right axilla and a small ulcer on the right index finger. He was mentally clear. There were 5.14 millions of erythrocytes and 11 thousand leukocytes per cubic millimeter, with a normal differential count. Hemoglobin was 11.5 Gm. A blood culture remained sterile. His serum agglutinated Bacterium tularense completely in 1:320 dilution.

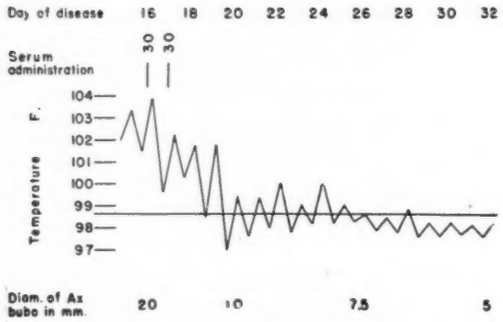

FIG. 1. *The effects of immune serum therapy on the temperature curve and the axillary bubo of a man with extensive pneumonia in the right upper lobe and inconsiderable pleurisy over the left lower lobe.*

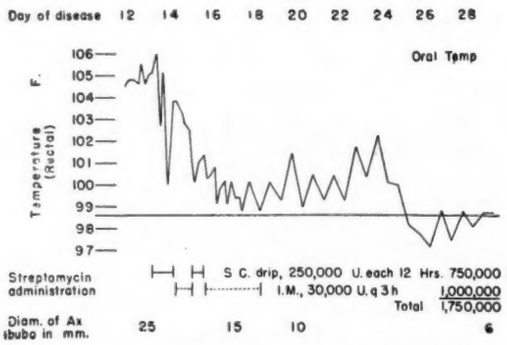

FIG. 2. *The effects of streptomycin therapy on the temperature curve and the axillary bubo of a desperately ill man with bilateral tularemic pneumonia who was admitted in a semicomatose state. Note the initial non-remittent fever at a high level.*

Immune horse serum was given intravenously in 30 cc. amounts on the sixteenth and seventeenth days of disease. The effects on the temperature curve and the axillary bubo are shown in Figure 1. There occurred an amelioration of general symptoms within twelve hours that was marked by the second day. This continued despite the advent of serum sickness during the night of the nineteenth day which brought a week of urticarial eruption and itching but little elevation of temperature. There was *x*-ray evidence of beginning resolution of the pneumonic exudate on the twentieth day but the degree of resolution was unchanged eight days later, at which time a thickened pleura with obliteration of the costophrenic angle was first observed in the left thorax.

The primary lesion healed on the nineteenth day of disease. He was out of bed on the twenty-ninth day, left the hospital on the thirty-second day and resumed work two weeks later. *Summary:* Durations of disease and of disability one and one-half months, of adenopathy 1 month; twenty-five days of fever, thirty-two days in bed, an ulcerated primary lesion for thirteen days, and a therapy-to-recovery interval of twenty-nine days.

CASE II. A. H., a machinist, aged forty-four, cleaned wild rabbits on November 27th. The onset occurred on November 30th with abrupt severe chill, fever, sweats, headache, severe malaise, cough, pain in the right axilla and in the tip of the right thumb. He was treated at home with sulfonamides and penicillin for eleven days. Pneumonia was present by the sixth day of disease, and for six days prior to admission his temperature fluctuated between 102° and 106°F.

He was admitted on the twelfth day of disease, delirious, disorientated, semicomatose, with non-remittent fever gradually increasing from 104.5° to 105.8°F. A history was not obtainable from the patient who could scarcely be aroused from his stuporous state for more than a few brief lucid moments at a time. Additional significant findings in this desperately ill man were physical and *x*-ray evidences of pneumonia involving all of the left lower lobe and part of the right upper lobe, moderate cyanosis, infrequent cough with tenacious mucoid, non-purulent, colorless sputum, a 2.5 cm. bubo in the right axilla and an ulcerated primary lesion on the tip of the right thumb. The liver and spleen were not palpable.

Blood cultures for Bacterium tularense and for other organisms remained sterile. Pneumococci were absent from the sputum, but Bacterium tularense was recovered from it by mouse inoculation. Serum agglutinin titers were 1:40 on the thirteenth day and 1:1280 on the eighteenth day.

Streptomycin therapy was begun on the thirteenth day of disease, giving ½ million units by hypodermoclysis during the first twenty-four hours. Administration was then changed to 30,000 units every three hours by intramuscular injection for the next twenty-one hours. Then ¼ million units were given by hypodermoclysis during the following twelve hours. Thereafter intramuscular injection of

30,000 units every three hours was resumed. A total of 1.75 million units was administered during a five-day period. The effects on the temperature curve and the axillary bubo are shown in Figure 2.

At the end of the first day of treatment the rectal temperature had fallen to 99.8°F., the man was sweating profusely and could be aroused to mental clarity for several minutes at a time. He remained somnolent, and as intermittent intramuscular administration at the rate of 240,000 units per day was substituted for the larger, continuous dosage he became less easy to arouse, the temperature rose and the cyanosis increased. Oxygen was administered, and as continuous streptomycin administration was resumed at the rate of 250,000 units in twelve hours the temperature fell again and, although somnolence persisted for several days, the patient was easily aroused at any time and gave intelligent responses. These gains were maintained throughout the second period of lower dosage, and improvement continued thereafter without interruption. Streptomycin was tentatively discontinued at the close of the fifth day of treatment. Although slight to moderate fever persisted for six days, the general improvement was so progressively satisfactory day by day that further treatment was deemed unnecessary.

On the day that therapy was discontinued *x*-ray films showed no change in the lung exudates but on the day the temperature fell abruptly to normal partial resolution was evident in both areas. Thereafter convalescence was rapidly progressive, hampered only by the healing of a decubitus that had developed rapidly during the semicomatose stage. *Summary:* Durations of disease and disability one and one-third months, of adenopathy 1 month; twenty-five days of fever, twenty-five days in bed, an ulcerated primary lesion for twenty-eight days, and a therapy-to-recovery interval of twenty-eight days.

Comment. The clinical responses to each agent were similar, prompt amelioration of symptoms of intoxication—headache, mental dulness or lethargy, sense of prostration, and severe malaise; reduction of fever and of the sizes of buboes, acceleration in the healing of ulcers and in the resolution of pulmonary exudates.

Although there are no significant differences between morbidity constants for these selected patients this result could not be duplicated by similar comparisons with unselected patients treated with serum. The responses to serum therapy have always exhibited greater variability than those that follow streptomycin therapy, even if treatment was given on the same day of disease to patients with apparently the same degrees of extent and severity of infection. Although serum sickness contributed appreciably to this result in half of all patients, it cannot account for similar variability among the other half. It seems probable that this striking difference is a reflection of the different modes of action of the agents, serum bacteriostatic only, streptomycin both bacteriostatic and bactericidal. The extraordinary variability of tularemia in untreated patients, in whom durations of disease range from two weeks to fifteen months, and occasionally longer, indicates that individual defense mechanisms differ enormously in the efficiency with which they react to invasion by Bacterium tularense. Since natural defense functions are impeded variably in degree and in duration by severe infections, it seems probable that the administration of a bacteriostatic therapeutic agent to a group of patients selected at random with respect to duration and severity of disease would result in considerable variability in therapeutic responses. In contrast, the administration of a bactericidal agent to a similar group would be expected to induce more uniform therapeutic effects since its mode of action is far more independent of the natural defense apparatus.

The therapeutic effects induced by the alternations of dosage in Case II are indicative of the approximate effective dosage

of streptomycin in tularemia of great severity. The latter was all that one could desire to test the efficacy of streptomycin therapy. The combination of a non remittent temperature at a high level with a semi-comatose state has for many years been for us the gravest prognostic sign and the most reliable clinical guide to the urgency of therapy, its quantity, rate or frequency of administration, duration and efficacy. Spontaneous recoveries of patients who have progressed to this status have been extremely rare. It was our opinion that this patient, if untreated, would not have survived for more than six days. From previous experience it was also judged that recovery as a result of heroic serum therapy was possible but unlikely. The results indicate that ½ million units of streptomycin per day for two days, followed by ¼ million units per day for an additional four days, a total of 2 million units, might well become the provisional basic dosage for human tularemia, to be modified as required by individual indications. Experience is too limited to judge what the optimal duration of administration should be. The temperature curve, together with the psychic state, will probably continue to be the best clinical guide to adequacy of dosage.

TABLE II

COMPARISON OF MEANS FROM CONTROL AND TREATED GROUPS

	Untreated N = 542	All Serum Treated N = 846	Immune Serum N = 792	Hyperimmune Serum N = 54	Streptomycin (Averages) N = 9
Duration of:					
Disease	3.78 ± 0.08	2.77 ± 0.04	2.82 ± 0.04	2.15 ± 0.11	2.39
Disability	3.12 ± 0.11	2.24 ± 0.04	2.28 ± 0.04	1.87 ± 0.10	2.16
Adenopathy	3.50 ± 0.10	2.46 ± 0.04	2.50 ± 0.03	1.78 ± 0.11	1.97
Fever	30.62 ± 0.88	27.55 ± 0.43	27.10 ± 0.47	28.91 ± 1.39	35.2
Bed days	46.86 ± 2.14	25.11 ± 0.49	25.23 ± 0.50	23.33 ± 1.38	31.4
Primary lesion	40.56 ± 2.12	32.35 ± 0.46	32.43 ± 0.48	30.95 ± 1.19	32.6
Therapy-to-recovery interval	.....	1.87 ± 0.04	1.89 ± 0.04	1.52 ± 0.09	1.67
Day of disease therapy was initiated	.....	23.32 ± 0.51	23.73 ± 0.53	17.22 ± 1.39	27.9

SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS OF CONTROL GROUP AND:

	All Serum Treated	D / P.E.d	Immune Serum	D / P.E.d	Hyperimmune Serum	D / P.E.d
Duration of:						
Disease	1.01 ± 0.09	11.84	0.96 ± 0.09	11.22	1.63 ± 0.13	12.21
Disability	0.88 ± 0.12	7.32	0.83 ± 0.12	6.98	1.25 ± 0.16	8.05
Adenopathy	1.05 ± 0.11	9.35	1.00 ± 0.11	9.26	1.72 ± 0.13	13.36
Fever	3.07 ± 0.98	3.13	3.52 ± 0.99	3.55	1.71 ± 1.65	1.04
Bed days	21.75 ± 2.20	9.89	21.63 ± 2.20	9.83	23.52 ± 2.55	9.24
Primary lesion	8.21 ± 2.17	3.79	8.13 ± 2.17	3.74	9.61 ± 2.43	3.95

The underlined figures are not statistically significant.

Comparison by Analysis of Groups. It was impossible to determine for all cases to what extent serum sickness increased the measurable aspects of morbidity. Hence no such attempt was made; the morbidity constants for all serum treated groups are inclusive of all effects of serum sickness. No serum had been refined, and the frequency of serum sickness was 51 per cent.

The morbidity constants from surviving patients of all groups are shown in Table II. The figures for the streptomycin series are averages. Although their significance cannot be expressed numerically, it is apparent that they compare favorably with those of the other treated groups. All differences are significant for the serum treated groups except those for durations of fever and of primary lesions, the latter escaping significance by a small margin. Note that the mean or average days upon which therapy was instituted were in either the third or fourth week of disease.

In order to show the importance of early therapy the total serum treated group was divided to compare the results of treatment administered during and after the first two weeks of disease. The early treated group was subdivided to compare the effects of treatment given during the first and the second weeks of disease. These figures, and the significance of their differences from the control group, are shown in Table III. Treatment after the second week failed to shorten significantly the durations of fever and of primary lesions, although all other aspects of morbidity were significantly reduced. Treatment given at any time during the first 2 weeks of disease effected highly significant reductions in all phases of morbidity. A separate test between the means from the subgroups treated during the first and the second seven days of disease, not included in the table, revealed no differences that approached significance.

The effects of the three agents in preventing suppurative adenitis are shown in Table IV. All patients who had experienced suppuration of buboes before therapy was

TABLE III

COMPARISON BETWEEN MEANS OF SELECTED DIVISIONS OF THE SERUM TREATED GROUP

	Treated after the 14th Day of Disease N = 493	Treated on or before the 14th Day of Disease N = 353	Treated during 2nd Week of Disease N = 206	Treated during 1st Week of Disease N = 147
Duration of:				
Disease	3.04 ± 0.05	2.41 ± 0.06	2.53 ± 0.08	2.25 ± 0.08
Disability	2.47 ± 0.05	1.95 ± 0.05	2.00 ± 0.07	1.88 ± 0.07
Adenopathy	2.68 ± 0.05	2.17 ± 0.06	2.24 ± 0.09	2.09 ± 0.09
Fever	31.61 ± 0.67	22.01 ± 0.48	22.87 ± 0.60	20.82 ± 0.71
Bed days	26.54 ± 0.68	23.24 ± 0.65	22.51 ± 0.85	24.26 ± 1.07
Primary lesion	35.25 ± 0.64	28.29 ± 0.60	29.32 ± 0.76	26.90 ± 0.97
Therapy-to-recovery interval	1.75 ± 0.05	2.01 ± 0.06	2.01 ± 0.09	1.88 ± 0.07
Day of disease therapy was initiated	35.02 ± 0.70	8.33 ± 0.13	11.53 ± 0.10	5.30 ± 0.10

SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS OF CONTROL GROUP AND:

	Treated after 14th Day	D / P.E.d	Treated before 14th Day	D / P.E.d	Treated in 2nd Week	D / P.E.d	Treated in 1st Week	D / P.E.d
Duration of:								
Disease	0.74 ± 0.09	7.99	1.37 ± 0.09	14.53	1.25 ± 0.11	11.51	1.53 ± 0.11	14.11
Disability	0.65 ± 0.13	5.20	1.17 ± 0.13	9.38	1.13 ± 0.13	8.45	1.24 ± 0.13	9.35
Adenopathy	0.82 ± 0.12	7.01	1.33 ± 0.12	10.93	1.26 ± 0.13	9.42	1.42 ± 0.14	10.11
Fever	0.99 ± 1.11	0.89	8.61 ± 1.00	8.59	7.75 ± 1.11	6.99	9.80 ± 1.13	8.68
Bed days	20.32 ± 2.25	9.04	23.61 ± 2.34	10.55	24.34 ± 2.30	10.56	24.34 ± 2.48	9.82
Primary lesion	5.30 ± 2.21	2.39	12.27 ± 2.20	5.57	11.23 ± 2.25	4.99	13.65 ± 2.33	5.86

The underlined figures are not statistically significant.

administered were excluded from the three treated groups. The rates for the serum treated groups show significant reductions in suppurative adenitis; that for the streptomycin treated group is not significant because of the small size of the group.

TABLE IV
COMPARATIVE FREQUENCIES OF SUPPURATIVE ADENITIS

	No. with Buboes	No. that Suppurated	Frequency Per Cent
Patients treated with:			
Untreated	480	268	56.0
Immune serum	746	202	27.1
Hyperimmune serum	49	13	26.5
Streptomycin	8	2	25.0

rate of 6 per cent showed that only the corrected rate for the immune serum group represented a significant reduction in mortality. No death occurred in the group treated with streptomycin.

Comparison of Therapy-to-Recovery Intervals. The foregoing comparative data may possibly be viewed by some, especially those who remember vividly the dramatic immediate improvement induced by streptomycin, with a suspicion of prejudicial manipulation of figures. It should be remembered that the estimations of durations of disease and of all other phases of morbidity were made by approximately 600 practising physicians, and that the tabulated constants represent the pooled judgments of this group. The cause of perturbance, if there be any, is the disease itself.

TABLE V
CRUDE AND CORRECTED MORTALITY RATES FOR THE COMPARED GROUPS

Clinical Types	No. of Cases	Total Deaths	Crude Mortality Per Cent	Corrected* Deaths	Corrected Mortality Per Cent
Immune Serum					
Ulceroglandular	722	29	4.0	13	1.8
Oculoglandular	23	1	4.3	1	4.3
Glandular	21	0	0	0	0
Typhoidal	66	10	15.2	2	3
Total	832	40	4.8	16	1.9
Hyperimmune Serum					
Ulceroglandular	48	3	6.3	1	2.1
Oculoglandular	1	0	0	0	0
Glandular	2	0	0	0	0
Typhoidal	9	3	33.3	1	11.1
Total	60	6	10	2	3.3

* Determined by excluding patients who were in the dying state when therapy was instituted. These deaths occurred within 96 hours from the first administration of serum.

The importance of the typhoidal type in relation to mortality is illustrated in Table v which shows mortality rates for the serum treated groups and the type fatality rates. The typhoidal type fatality rate is normally four times that of any other type. A test of the rates against an assumed fatality

It will be noted in Tables II and III that the therapy-to-recovery intervals varied but little regardless of the nature of the therapeutic agent, and notably irrespective of

the time at which it was administered, whether early or late. The inescapable conclusion is that it required on the average 1.8 months to effect recovery from tularemia, and that this period was not shortened significantly more by one agent than by any other, nor by treatment very early in the course of disease. These relations are shown graphically in Figure 3. The average interval from therapy to recovery was fifty-five days, with extremes of forty-six and sixty days. This period represented the time needed by patients, treated with either bacteriostatic or bactericidal agents, to repair pathologic lesions and to restore pathologic physiology to the extents that symptoms and disability disappeared. The pathologic features that most frequently prolong convalescence are liquefaction necrosis of lymph nodes, pneumonic lesions and their sequelae, and lesions of the serous membranes. It is unknown to what extent foci of necrosis, possibly scattered widely as results of the early primary bacteremia, contribute to prolongation of convalescence. Reports of necropsies following accidental deaths during convalescence are too few to be more than indicative. One on the fifty-fourth day of normal temperature, one day less than the average period of induced convalescence, revealed no trace of the recent infection.[3] Another, on the third day of normal temperature when vigor and competence were returning rapidly, disclosed numerous foci of necrosis in the liver and spleen, and complete liquefaction within their capsules of many mesenteric and intra-abdominal lymph nodes.[4] Since the disease had been of less than usual severity it is not unlikely that the pathologic findings are fairly representative of tissue changes at this stage of recovery. It seems apparent that the pathologic lesions impose limits on what may be expected from therapy in tularemia, and that with agents presently available this means an average

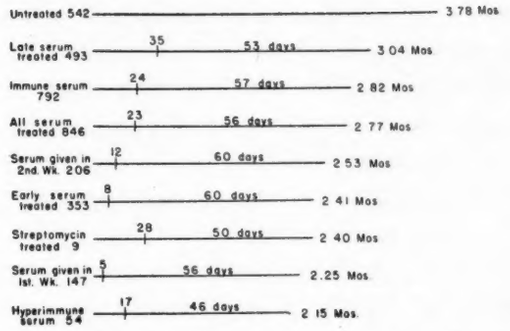

Fig. 3. The parallel lines, drawn to scale, represent the mean durations of disease for all groups. The short vertical cross lines, with superimposed numbers, indicate for the treated groups the mean days of disease upon which therapy was administered. The parts of the horizontal lines that lie to the right of the cross lines represent the therapy-to-recovery intervals.

convalescence period of fifty-five days after their administration. The earlier the patient is treated, by so much will convalescence be shortened.

Figure 3 shows that only three modes of therapy reduced the duration of disease to less than a mean of 2.5 months: treatment with immune serum before the ninth day of disease, and treatment with either hyperimmune serum or streptomycin. The only agents that effected this result when they were administered later than the second week of disease were streptomycin and hyperimmune serum.

It is doubtful in my opinion if serum therapy can do better. If hyperimmune serum were to be refined, the slight reduction that might occur in the length of the therapy-to-recovery interval would probably represent the mean days of illness spared from serum sickness. The bactericidal action of streptomycin, the high susceptibility of Bacterium tularense to it, and the clinical responses of individual patients justify the expectation that this agent will terminate the progression of many more advancing lesions more rapidly. As its availability increases and as greater skill in administration is developed, it may be anticipated that its use will diminish the

length of the therapy-to-recovery interval to the limits imposed by pathogenesis and pathology. While waiting with interest to learn what these limits will prove to be, it may be noted that the small initial experience already provides a basis for an assumption that some reductions in all aspects of morbidity over those obtainable with hyperimmune serum, except those dependent upon suppurative adenitis, may be expected and that streptomycin is unquestionably the agent of choice for the desperately ill patient.

A recommendation previously made,[1] that all patients with tularemia do not need serum therapy, is equally true with respect to streptomycin. This opinion is based on the nature of the disease in man and on clinical judgment acquired by experience. Many ambulatory patients are first seen after they have weathered the initial severe phase, with no discoverable visceral lesions, little or no fever, receding buboes and primary ulcers that have reached maximal size. The worst that could be expected would be eventual suppuration of a bubo, and neither streptomycin nor serum therapy has prevented all suppurative adenitis. Although Figure 3 shows that treatment with either agent at this stage will, on the average, shorten convalescence somewhat, it has long been apparent to those who are familiar with the disease that the little that can be so achieved for the individual is seldom worth the cost or some other ancillary aspect of treatment. The deceptive features of tularemia that require prompt recognition and adequate therapy to forestall serious consequences are manifested almost always during the first fifteen days of illness, seldom or rarely thereafter, and practically never in the type of patient described above.

SUMMARY

Treatment of tularemia patients with immune serum before the end of the second week of disease induced significant reductions in mortality and in all aspects of morbidity. Greater reductions in morbidity were effected by treatment with hyperimmune serum or streptomycin. Of the agents studied only streptomycin and hyperimmune serum reduced the mean duration of disease to less than 2.5 months if treatment was given later than the second week. A comparative study of therapy-to-recovery intervals indicated that the nature of the disease imposed limits on the results obtainable by all forms of therapy. The study suggests that these limits have been just about reached with respect to serum therapy but not with respect to streptomycin therapy. It also indicates that future comparisons should demonstrate a superior effectiveness of streptomycin in diminishing morbidity; and, since it is already shown to be a better agent for treatment of the desperately ill patient, that streptomycin will become the treatment of choice for tularemia.

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Combined Staff Clinics

Bronchial Asthma

These are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ROBERT F. LOEB: Bronchial asthma is a common human affliction which, as you know, results basically from an allergic response and is characterized by spasm and edema of the bronchi. Significant advances have been made in our understanding of the immunological and physiological mechanisms involved, and in the management of this disorder. It is the purpose of this clinic to integrate this knowledge in order to obtain a clearer view of the problems presented by the asthmatic patient. Dr. Cross will present an illustrative case.

DR. RICHARD J. CROSS: This is the second medical admission of a thirty-eight year old white housewife because of asthma of twelve years' duration. Personal history and system review are non-contributory. Her mother died at the age of fifty-two with severe bronchial asthma. There is no other family history of allergy.

The present illness began just over twelve years ago at which time the patient was under great physical and emotional strain caring for her dying mother. She developed a chronic, non-productive cough and for two weeks had some pleuritic pain on the right. Then, shortly after her mother's death twelve years ago, she started having attacks of wheezing dyspnea diagnosed by her doctor as asthma. These were typical asthmatic attacks except that she had even more difficulty with inspiration than with expiration. The patient averaged two to four attacks a day, each episode lasting several hours unless treated with adrenalin which gave prompt relief. This condition cleared spontaneously after three months. She was then perfectly well until ten and one-half years ago when her asthma recurred for one month just prior to her marriage. Her next bout occurred two years later when she was four months pregnant. Ten days following delivery (under ether anesthesia) she developed a cough productive of foul sputum and was found to have an abscess of her right upper lobe. This was treated here and responded promptly to postural drainage, her asthma subsiding also. The patient was then symptom-free for seven years during which her second child was born. One year ago, when four months pregnant, she had a recurrence of her asthma which has persisted almost constantly to the present.

A careful review of her history has failed to uncover any specific allergens. Routine skin tests done here eight years ago were all negative. Other tests done six months ago are reported to have shown her to be sensitive to eggs, peanuts and cheese and since this time she has noticed that these foods seem to precipitate attacks. She also believes that she is sensitive to penicillin.

Physical examination revealed little of significance except the findings referable to asthma. There was marked difficulty with respiration, with a loud wheeze on both inspiration and expiration audible throughout the lung fields, and many coarse rhonchi. Fremitus was normal, as were the voice and breath sounds. There were no crepitant râles. A soft liver edge was palpable just below the right costal margin.

The blood count was normal except for an eosinophilia of 9 to 13 per cent. Urinalysis was normal. The blood Kline test was negative. The sedimentation rate was 3 mm. per hour. Sputum examination revealed no acid-fast organisms and on culture only Streptococcus viridans. The stool was guaiac negative and contained no ova or parasites. A nasal smear showed many eosinophiles. Blood for cold agglutinins was positive in a dilution of 1–32. *X*-ray examination of the chest disclosed an irregular increase in density just above the right hilum. Both antra showed considerable thickening of the lining membrane. Skin tests were not done. Pulmonary function studies will be described by Dr. Baldwin.

The patient was given aminophyllin 0.1 Gm. three times daily by mouth, epinephrine 0.2 cc. hypodermically every two hours as needed, and benadryl 250 mg. a day in four doses. During her hospital stay she has had regularly three or four asthmatic attacks a day which respond promptly to epinephrine injections. Benadryl has apparently been of no value. In the past she has received ephedrine by mouth with minimal effect, vaponephrine spray with slight effect, aminophyllin by rectal suppository which was moderately effective, and aminophyllin intravenously which helped relieve her worst attacks. Epinephrine has always been the most effective agent for stopping any given attack.

In summary, this patient is presented as a case of recurrent bronchial asthma of undetermined etiology.

DR. LOEB: I have asked Dr. Beatrice Seegal to review for us the processes involved in sensitization of the bronchial tree.

DR. BEATRICE C. SEEGAL: This patient apparently has no history of sensitivity to explain the asthma. However, sensitivity to a specific allergen frequently is the cause of asthma. In order to understand the allergic mechanism in asthma we depend largely upon animal experimentation.

I know that our old students will recall the picture of anaphylaxis in the guinea pig which they saw in the laboratory. You will remember that we examined guinea pigs which had survived diphtheria toxin due to treatment with antitoxin. These animals had received approximately 0.01 cc. of horse antitoxic serum. Three weeks later we injected them intravenously with a fraction of a cc. of horse serum. They exhibited slow, labored respiration, became cyanotic and died within about three minutes. The cause of their death was apparent on examination of the lungs which were emphysematous and failed to collapse when the chest was opened. The reason for this was evident on histological examination. As in the case of asthma in man, the bronchioles were constricted due to contraction of the smooth muscle, and the mucosa was thrown into folds, further obstructing the lumen. The strong inspiratory suction drew air into the alveoli which were found greatly distended, but during expiration all this air was not expelled and asphyxiation soon resulted as the lungs expanded to the limit of the thoracic cavity.

Bronchiolar constriction may be obtained in other species of animals following sensitization. Drs. Sollmann and Gilbert have examined fresh slices of lung taken from sensitized rabbits. These pieces of tissue were placed in Ringer-Locke solution and the effect of the addition of a specific antigen observed under the microscope. When the antigen was added to such a preparation the lumen of the bronchioles narrowed. After a few minutes of constriction the muscle relaxed and the lumen expanded again. Further additions of antigen produced no effect.

Of course, sensitization in man does not usually occur by the parenteral injection of antigen. Natural routes of sensitization are

by inhalation, ingestion or dermal contact with the allergen. Dr. Ratner placed guinea pigs in an atmosphere containing horse dander for a brief period of inhalation; when these animals were rested for a few weeks without further exposure and then returned to an atmosphere containing horse dander they developed respiratory difficulty typical of an attack of asthma. This occasionally resulted in fatal asphyxia.

The evidence indicates that experimentally induced allergic reactions are due to an antigen-antibody reaction. Allergens are also antigens. The incubation period for the development of sensitivity is the same as that necessary for the development of antibodies. Only the specific antigen used to sensitize elicits the reaction; in other words, the reaction is specific. Furthermore, the serum of sensitive animals will passively sensitize normal animals to the appropriate antigen. The capacity of the serum to produce sensitivity is correlated with its precipitin titer. We should see a similar immunological mechanism in asthma. However, no *in vitro* demonstration of antibodies in the serum of asthmatics or of other allergic individuals has been accomplished. Nevertheless the serum contains a substance (antibody?), referred to as a reagin, which is capable of passively sensitizing a normal human subject. Reagin may be diluted several hundred times and still transfer sensitivity to the skin of a normal individual.

A few years ago we would have been unable to offer any explanation for the failure to demonstrate antibody in the serum of an allergic individual. In the last few years, however, two pieces of work have added to our understanding of the immunological factors in human allergy. The first of these, carried out by Dr. Kabat and his associates, consists of a quantitative study of the amount of antibody necessary to sensitize a guinea pig passively. They found that as little as 0.03 mg. of antibody N when injected intravenously into the guinea pig was sufficient to sensitize all animals so that a subsequent injection forty-eight hours later of 1 mg. of antigen produced fatal anaphylactic shock. This amount of antibody is inadequate, when diluted in the total body fluids, to permit detection by *in vitro* antibody tests. It is therefore not surprising that a patient may be acutely allergic and yet such antibodies may not be demonstrable in the serum. The *in vivo* passive sensitization test is more sensitive than the *in vitro* test.

Another series of observations which promises to throw light on the immunological mechanism of allergy was initiated by the work of Dr. Cooke and carried on by his associates, particularly Dr. Loveless. She has shown that the reagin or sensitizing antibody in the serum of ragweed hay fever subjects is thermolabile, being destroyed by heating to 60°C. for one-half to one hour. This antibody is found only in the serum of naturally allergic individuals. It cannot be induced by immunizing normal individuals with pollen. On the contrary, they develop a thermostabile antibody which does not sensitize passively and which actually prevents the specific allergen from initiating an allergic reaction in a sensitized area. When an allergic patient is treated by the injection of a specific allergen production of both the thermolabile reagin and the thermostabile antibody substance is stimulated. The clinical improvement of the patient, which is associated with decreasing skin and eye sensitivity, is roughly proportional to the amount of thermostabile antibody found in the circulation. It may be that the difference between an allergic individual and one who fails to develop allergy depends upon the capacity of the former to produce a thermolabile sensitizing reagin.

DR. LOEB: With regard to the specificity of allergens precipitating bronchial asthma, many patients at first are sensitive to a recognizable specific allergen but subse-

quently become increasingly sensitive to an ever widening group of agents.

DR. ALVAN L. BARACH: Most patients sensitive to dust fall in this category. Some patients begin with a specific allergy to ragweed and later become sensitive to house dust. Dust sensitivity is usually secondary.

DR. LOEB: Such agents probably act as non-specific irritants. Dr. Baldwin's findings help explain why asthmatic subjects, apparently well between attacks, are nevertheless particularly sensitive to non-specific irritants of this kind. Dr. Baldwin will review briefly for us certain factors involved in the normal respiratory mechanism and also the deviations observed in the asthmatic state and between asthmatic attacks.

DR. ELEANOR BALDWIN: The asthmatic state is one of acute ventilatory insufficiency, in which the patient's main difficulty is in moving the air in and, particularly, out of the chest. Before discussing the pathological physiology of asthma it seems worth while to remind you of certain anatomical and physiological factors which are important in understanding the mechanism of respiratory motion and ventilation of the lung.

Sir Arthur Keith, in 1909, described two groups of respiratory movements which he called upper costal and costo-diaphragmatic. The structures concerned with the upper costal movement are the bony structures and muscles of the neck and shoulder girdle, the upper two thirds of the sternum and the first five ribs and vertebrae, which move the anterior chest forward and upward during inspiration, allowing the two upper lobes to expand. The fifth to tenth ribs and vertebrae, the diaphragm and the abdominal muscles are concerned in the costo-diaphragmatic movements. The ribs, due to their downward, outward and backward takeoff from the spine, and their downward and forward slant, allow the chest to expand laterally during inspiration; while the diaphragm, because of its higher anterior insertion, enlarges the chest in the forward as well as in the downward direction. Thus the lower lobes are able to expand in all three directions during inspiration.

The diaphragm is the most powerful muscle of respiration. It has been found that a descent of 3 cm. of the diaphragmatic leaves increases the chest capacity by approximately one liter.

During inspiration, the bronchial tree, due to its elasticity and distensibility, not only elongates but also dilates; and conversely, it constricts and shortens during expiration. Thus the bronchial tree is most widely patent in the deep inspiratory position, which is the one most commonly assumed during an asthmatic attack. The relationship between the size of the muscular bundles in the larger as compared with the smaller bronchial passages, also, has an interesting relationship to the asthmatic state. In bronchi 10 mm. in diameter, the surrounding muscle has a thickness of 0.2 mm.; while in bronchi 1 mm. in diameter, the muscle bundles have a thickness of 0.1 mm. Thus it may readily be seen that bronchiolar muscle spasm and hypertrophy in the smaller bronchioles may well cause either a partial or complete obstruction of a lung lobule.

As you all know, the intrapleural pressures during quiet respiration are negative, due to the force of the elastic contractility of the lung. During quiet inspiration the pressures are in the neighborhood of −3 to 6 mm. Hg.; during expiration they rise to − 1 to 3 mm. Hg. If inspiration is forced and obstructed, as by forceful breathing through pursed lips, the pressure may drop to − 40 mm. Hg.; and conversely, during forced expiration as in coughing it may rise to + 50 mm. Hg.

Finally, I would like to explain briefly the physiological measurements to be mentioned in the ensuing discussion:

1. The *total lung capacity* is a measure of the air-containing tissue in direct communication with the bronchial tree. The fixed air of the lung, which is called the *residual air*, normally is less than 30 per cent of the total lung capacity. A residual air: total capacity ratio over 36 per cent indicates relative hyperinflation of the lung, usually associated with diffuse emphysema.

2. The ability of the individual to move air in and out of the chest in a unit of time, or his *ventilatory capacity*, is determined by the efficiency of the bellows action of the chest. This is dependent upon good neuromuscular coordination of the respiratory muscles and joint movements, upon a patent tracheobronchial airway and upon the elasticity of the lung. The *maximum breathing capacity*, expressed in liters per minute, is the measure of the maximum voluntary movement of air in and out of the chest during a period of time and is, therefore, a measure of the bellows action of the chest.

3. It is now generally accepted by pulmonary physiologists that in normal subjects ventilation is unequally distributed to various parts of the lung. Thus, after a subject has breathed 100 per cent oxygen for a seven-minute period his alveolar air collected during forced expiration will contain a certain amount of nitrogen which has not been washed out of the inadequately ventilated areas of lung during the period of quiet oxygen breathing, but which contributes to the alveolar sample during the forced expiration. In individuals without pulmonary disease the nitrogen per cent of the alveolar air or the *index of intrapulmonary mixing* seldom exceeds 2.5 per cent after a seven-minute period of oxygen breathing. A high nitrogen per cent of the alveolar sample taken after oxygen breathing is always an indication of poor intra-alveolar ventilation, although a normal value does not necessarily rule out the presence of this impairment of function since seven-minute period of ventilation may be more than sufficient to wash out a small amount of residual air.

During an asthma-free period the asthmatic subject feels well and goes about his business without complaint. Even upon the most thorough physical examination it is rare to find any demonstrable disorder. However, when the pulmonary function of these individuals is examined by submitting them to a series of tests, an abnormal respiratory pattern is found, with several of the stigmas of ventilatory dysfunction. In Dr. Cournand's laboratory at Bellevue and in ours in this hospital, we have had the opportunity of studying ten asthmatic subjects at a time when they were free from symptoms. The following significant findings were observed in all cases:

1. A normal total lung capacity with normal distribution of air. In no case was there any evidence of pulmonary distention as determined by an increased residual air: total capacity ratio.

2. All but one patient presented marked impairment of the bellows action of the chest as demonstrated by a decrease of the maximum breathing capacity from the predicted value for the individual subject. The mean maximum breathing capacity for this group of ten asthma-free subjects was 58 per cent of the predicted value. That this impairment of ventilatory capacity was in part due to bronchiolar spasm is indicated by the improvement of the maximum breathing capacity of all ten subjects following the use of a bronchodilator spray. The mean maximum breathing capacity for the group following the bronchodilator drug was 81 per cent of the predicted value.

3. Hyperventilation was noted during rest, a minute of standard exercise and the first minute of recovery.

4. In every case the alveolar nitrogen following oxygen breathing was abnormally high. The mean value for the group was 4.5 per cent.

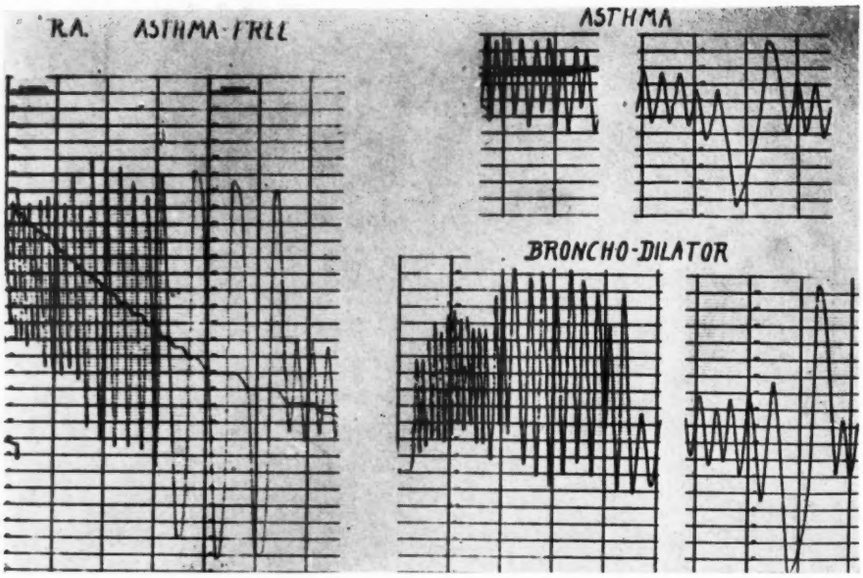

FIG. 1. *Spirograms. Left, R.A. during asthma-free period, showing essentially normal respiration. Right above, R.A. during asthmatic attack. There is a decrease in amplitude, in forced maximal expiration (vital capacity), and during maximum rapid ventilation (maximum breathing capacity). There is also a decreased number of breaths during a unit period of time in the maximum breathing capacity test. Right below, R.A. during asthmatic attack, after the use of a bronchodilator drug. Both the amplitude and rate tend to return toward normal.*

5. All subjects presented a normal oxyhemoglobin saturation at rest and following exercise, and normal oxygen consumption during all the periods of observation; this indicated normal respiratory gas diffusion across the alveolo-capillary membrane and a normal pulmonary blood flow.

Thus these individuals who were symptomless and apparently healthy, but subject to asthmatic attacks, present very definite evidence of ventilatory dysfunction which, however, was not of sufficient magnitude to produce symptoms or physical signs at rest or upon ordinary exertion.

When an acute asthmatic attack arises, a state of acute ventilatory insufficiency develops. The subject assumes a state of persistent hyperinflation since it is only in this position that the narrowed bronchial passages can be sufficiently dilated to permit adequate ventilatory air exchange. The anterior chest is raised forward and upward and the accessory muscles of respiration of the neck and shoulder girdle are called into play and are often steadied by the patient resting his weight on his hands. The diaphragm is flattened and can no longer descend upon inspiration. It therefore contracts horizontally, pulling the lateral ribs inward and the lower sternum backward. Thus the ventilation is almost wholly upper costal since the costo-diaphragmatic component is ineffectual. During the forced and difficult inspiration the intrathoracic pressure becomes highly negative, which favors the filling of the pulmonary blood vessels but makes more difficult the filling of the left heart. For this reason the peripheral arterial pressure is very apt to fall during severe asthma.

We had the opportunity of studying the lung volume of a patient who was developing an asthmatic attack. Although her vital capacity remained unchanged, the residual air, and therefore her total capacity, increased by 900 cc. with a concurrent increase of the residual air: total capacity ratio. In a more severe asthmatic state the

vital capacity and maximum breathing capacity become decreased. The latter shows a decrease not only in amplitude of the respiratory excursions but also of the number of breaths in a given period of time. Following the use of bronchodilator drug a marked increase of both vital capacity and maximum breathing capacity occurs, since the obstruction caused by the bronchiolar spasm is relieved. This train of events is seen in Figure 1 and Table 1, which represent the observations made in a young asthmatic during an asthma-free and an asthmatic period.

STUDENT: The asthmatic patient described by Dr. Cross experienced more difficulty with inspiration than with expiration.

DR. CROSS: That was the history she gave. However, we had the opportunity of observing her in acute attacks and found that while inspiration was labored, her chief difficulty was in the expiratory phase.

STUDENT: I should like to ask about another point in the patient's history. She developed a lung abscess which responded to medical treatment. This episode was followed by freedom from acute asthmatic attacks for many years. Are not infections of the lungs likely to predispose to bronchial asthma?

DR. LOEB: Yes, but it is a common experience that a serious infectious process or operative procedure may be followed by freedom from asthma for variable periods of time.

DR. FRANKLIN M. HANGER: There is an interesting relation of infection to hypersensitivity. Animal experiments have demonstrated clearly that infection alters the immune response to allergens.

DR. LOEB: We shall turn now to a consideration of the management of the asthmatic patient. Dr. Atchley will discuss certain aspects of this problem and Dr. Barach will follow with methods of treatment of status asthmaticus.

TABLE 1

NORMAL VALUES OF PULMONARY FUNCTION TESTS, AND VALUES FOR ASTHMATIC SUBJECT R.A. DURING AN ASTHMA-FREE PERIOD AND DURING AN ASTHMATIC ATTACK, BEFORE AND AFTER A BRONCHODILATOR DRUG

	Pulmonary Function			
		Asthmatic Patient R.A.		
	Normal Subject	In Asthma-free Period	During Asthmatic Attack	
			Before Bronchodilator	After Bronchodilator
A. *Ventilatory tests*				
Resting ventilation, liters/min	6.00	6.80		
Vital capacity, liters	5.00	4.95	2.00	3.50
Residual air, liters	1.20	1.30		
Total capacity, liters	6.20	6.25		
Residual air/total capacity × 100	19.4	20.8		
Maximum breathing capacity liters/min.	150.0	81.0	19.0	49.0
Index of pulmonary mixing: alveolar N, % after 7 minutes oxygen	<2.5	2.9		
B. *Respiratory tests*				
Arterial oxygen saturation %				
Rest	95			
Exercise	96	.....	94.2	

DR. DANA W. ATCHLEY: The asthmatic response belongs essentially to the field of internal medicine and every internist should qualify himself to treat it. While the allergist plays an important rôle in fostering investigation and in the care of unusually difficult cases, allergy is only one of the several mechanisms which combine to produce an attack. As the specialist is concerned chiefly with integrating the multiple components which constitute the individual as a whole, the internist therefore should, in most instances, assume the major responsibility for

treating this disease. He will happily call on the allergist for assistance more or less frequently as his experience grows, but he should not automatically transfer every patient as soon as he hears a wheeze.

In no disease is there a closer correlation between analysis and therapy. Proper management is based not only upon an understanding of the participating forces and their relative values, but treatment often is so obvious a corollary of the investigation that no formal therapeutic suggestions are necessary. Every study of an asthmatic patient should be accompanied by as complete an education of the patient as his intelligence will permit. The various factors should be explained to the patient and the procedures by which they are discovered and eliminated. The trained observation of the asthmatic himself is an invaluable asset, both in diagnosis and treatment. This point of view is, of course, merely another expression of the increasing realization that the proper treatment of disease is predicated more safely upon the understanding of the patient than upon his obedience.

The allergic response is the basic factor in asthma. When this is the result of a single antigen, easily eliminated, the most satisfactory patient-physician relationship in all of medicine ensues. Unfortunately, these delightful situations are rare and a search for the responsible agents is difficult and often completely unsuccessful. The first step, and by far the most important in such an appraisal, is a careful history: a search for correlation of the attacks to season, to environment, to new objects introduced into the household, to pets, etc., requires patience on the part of the physician, and informed cooperation on the part of the patient. Many interviews may be necessary.

The next step consists of application of the method of trial and error by experimental control of the environment with observation of effects on the asthma. A pet may be removed or the patient transferred to another location. Foods may be omitted or furs put away. An apparently positive result requires repeated checking because coincidence plus wishful thinking often gives false results. If these methods fail, skin tests are indicated although they are in general disappointing. When first introduced, the skin-testing technic led to high hopes for an easy solution of all allergic responses, but as experience grew it became apparent that the reliability of this method is limited. Antigens with negative skin test give asthma at times, and many substances with high skin reactivity produce no effect on the bronchial tree. It is important to remember these facts when there are numerous positive results and to confirm the skin tests by careful clinical experimentation. Many patients have been subjected to wholly unwarranted and even harmful restriction because of uncritical use of the reports from a series of skin tests.

When an antigen is clearly responsible for asthma, every possible attempt to eliminate it from the environment should be encouraged. Desensitization is so unsatisfactory that it should be only a last resort in a situation otherwise insoluble.

Next to allergy comes respiratory infection as a fundamental cause of asthma. It is unnecessary to discuss theoretical considerations in relation to the relative importance of bacterial allergy and bronchial disease as the basis for the importance of respiratory infections in this field. Whatever the final answer, the fact remains that practically all asthmatics require a careful search for disease in the respiratory tract and its elimination, if possible. A nose and throat consultation, *x*-rays of sinuses and sputum cultures should accompany a thorough investigation into the patient's respiratory history. Spectacular benefit may follow the

removal of polyps or the clearing of a chronic empyema of the antra. Penicillin administration when susceptible organisms are found in the sputum is helpful with some patients. Vaccines as a preventative or curative measure have little sound scientific support, although patient testimonials are common. When children with an asthmatic tendency are subject to respiratory infections in one climate and are free in another, it is wise to follow this lead in management.

Allergy and respiratory infections are the important basic mechanisms in the causation of asthma, but there are several contributory factors that may be crucial to the relief of this disease. In fact, asthma may be latent when these contributory factors are properly controlled, and constantly recurrent when they are not. The most important of these is the influence of the emotions. Some psychiatrists consider asthma as a wholly psychosomatic phenomenon and suggest that the psychodynamic pattern of the asthmatic is a characteristic one. Although the internist may not go as far as this, he readily admits that with all other variables apparently constant, asthma can appear following an emotional trauma. Moreover, there is often a clear correlation between the relief of anxiety and the release of bronchial obstruction. The physician who neglects the emotional problems of his patient will fall short of his maximal therapeutic potentialities in asthma. It is occasionally necessary to rely on a psychiatrist for solution of this component.

Pulmonary irritants such as dust, fumes, smoke or cold air, may act as a trigger mechanism for an attack. The chronic asthmatic should not smoke; he should avoid dusty train or automobile trips; he should move out when his house is being cleaned or painted. Occupational exposure to these hazards should be explored.

Another stimulant of an attack in the susceptible is exertion. The amount required depends on the severity of the underlying process; even laughing may sometimes be a precipitant and coughing often contributes.

There is insufficient time for me to discuss in detail the various medications used to prevent or relieve asthma, such as adrenalin, ephedrine, aminophylline and iodides. There is, however, one fundamental principle that is essential: no patient should carry out his treatment blindly. Every effort should be exerted to instruct him in the reasons for the medication, the results expected, the methods of observing and regulating its application, so that he will never be bothered with drugs that do not help and will also never fail to derive the maximum efficiency from those that do. No one can accomplish this as well as the patient himself if he is taught both the necessary facts and a few elementary principles of critique.

It should be apparent from the foregoing discussion that the proper treatment of asthma is dependent upon a well balanced analysis of the individual and his environment. The program of management derived from such an analysis must be a blend of scientific knowledge and of common sense and must be uniquely adapted to the particular asthmatic patient under consideration.

DR. BARACH: The procedures used in the therapy of status asthmaticus are listed in Table II, together with the physiological basis on which each depends.

Before beginning treatment a brief but searching inquiry into the previous history of the patient is important in order to make, if possible, an etiological diagnosis. A seasonal incidence of asthma may indicate that the condition was precipitated by grass or ragweed pollen, in which case inhalation of filtered air may bring about prompt recovery. Patients may also develop asthma in the Fall after the pollen season is over, due to unsuspected circulation of dust when the steam heat is first turned on in apart-

ments with boxed-in radiators. Dust collects on these radiators, in many cases for years, because of the difficulty in cleaning them. A similar provocation may take place in houses with central hot-air heating in which dust enters the floor through grills from ducts that are almost impossible to clean.

TABLE II
TREATMENT OF STATUS ASTHMATICUS

Procedures	*Based on:*
Continuous inhalation of 50% oxygen	Prevention of respiratory failure; alleviation of functional emphysema
Intermittent helium-oxygen inhalation	More efficient ventilation of alveoli at lower effort
Positive pressure respiration	Maintains increased patency of bronchi; also for pulmonary edema
Continuous nebulization of 1:100 epinephrine and 1% neosynephrin	Aids expectoration and bronchodilation
Aminophyllin 0.48 Gm. i.v. or i.m. Aminophyllin 0.6 to 0.7 Gm. rectally	Bronchial relaxation if refractoriness is absent
Curtailment of adrenalin and aminophyllin	Responsiveness to these drugs returns if temporarily stopped
Demerol 50, 75 or 100 mg. hypodermically for acute paroxysms	Bronchial relaxation obtained when refractory to aminophyllin
Potassium iodide—4 cc. daily	Loosens mucus by increased secretion
Bronchoscopic suction	Eliminates plugs in larger bronchi
Ether anesthesia	Bronchial relaxation for persistent spasm
Dilaudid gr. $\frac{1}{64}$ to gr. $\frac{1}{32}$ not more often than twice daily	Bronchial and central nervous system relaxation, but guard against respiratory depression
Filtered air	For pollen asthma
Fever therapy	Desensitization if patient's condition warrants it
Antibiotic therapy	For infection due to pneumococcus, hemolytic streptococcus, staphylococcus aureus and at times Streptococcus viridans
Manual elevation of the diaphragm	Empty over-distended lungs

Allergic reactions to horse hair in mattresses and in upholstered furniture are sometimes of such severity as to maintain persisting bronchial spasm when more obvious offending agents, such as feathers, have been excluded.

In the majority of cases of status asthmaticus occurring in middle life or in older people, infection is the usual pathogenetic factor. Whatever the theory of infectious asthma may be, it is common experience to witness the onset of status asthmaticus after a cold or a bronchial infection. Culture of the sputum is of value in these cases, since infection with hemolytic streptococcus, pneumococcus and staphylococcus aureus may respond promptly to penicillin treatment. In a few cases in which Streptococcus viridans has been isolated, antibiotic therapy has been followed by clearing of the symptoms of bronchial spasm, although the majority of patients with non-hemolytic streptococcus in nasal, throat, or sputum cultures do not show significant benefit from penicillin treatment. Granted that we have attempted to make an etiological diagnosis as carefully as can be done, we are then in a position to employ treatment for the disturbed physiological functioning in the bronchi and lungs that takes place in status asthmaticus.

The continuous inhalation of 50 per cent oxygen is designed to prevent respiratory failure due to anoxia and to decrease the functional over-distention of the lungs that takes place in these cases. Administration of oxygen enriched atmospheres is prescribed not for the purpose of relieving dyspnea primarily, but to decrease the volume of breathing so that additional opportunity is afforded to the patient to empty over-filled alveolar cells during expiration. The oxygen tent, or a rubber catheter inserted into the nasal or oral pharynx, may be employed to achieve adequate oxygen treatment. The mask is not suitable for continuous oxygen therapy in this condition, since even slight resistance encountered during inhalation of oxygen in a mask is apt to provoke sufficient discomfort to result in refusal of the patient to continue with it. The duration of oxygen treatment depends upon the length of time required for other measures to produce adequate bronchial relaxation; in most

cases five to seven days of continuous oxygen therapy is indicated.

Helium-oxygen mixtures of 75 to 80 per cent helium and 25 to 20 per cent oxygen are given intermittently to promote more efficient ventilation of the alveoli with decreased physical effort. Bronchial relaxation may be gradually obtained as a result of inhaling such a mixture for half an hour to one hour four or five times a day. This is best used with the Meter mask, the inspiratory valve being removed, with a flow of 5 to 7 liters per minute from the helium-oxygen cylinder. The helium-oxygen hood makes it possible to administer this lighter-than-air gas with positive pressure as well, but it is conveniently employed only in a hospital in which adequate technical supervision is available. The length of treatment with helium-oxygen mixtures is generally four to five days.

Positive pressure respiration, in which pressure is maintained both during inspiration and expiration, increases the patency of the bronchi. Administered by a positive pressure hood, it is a comfortable method of decreasing the effort of breathing and maintaining better ventilation. When pulmonary edema takes place as a complication, pressure breathing is best used both in inspiration and in expiration but it may be more conveniently employed by a mask in which expiration takes place through a resistance or under 4 or 5 cm. of water pressure. The pressure mask used during the war at high altitudes with a demand regulator may soon be available for administration not only of continuous positive pressure but also of intermittent positive pressure in the treatment of bronchial asthma and pulmonary edema.

Inhalation of helium with oxygen and pressure breathing have both been shown to decrease the pathologically elevated negative pressure that occurs in respiratory obstruction during the inspiratory cycle. In one patient with severe status asthmaticus, the intrapleural negative pressure at the end of inspiration was reduced from −27 to −17 cm. of water during the inhalation of 80 per cent helium and 20 per cent oxygen under a positive pressure of 6 cm. of water. The pathological changes in the lungs in obstructive dyspnea may be traced to the heightened negative pressure within the lungs, which is responsible for increased exudation of serum into the alveoli, and congestion and edema in the bronchial mucous membrane. Circulatory insufficiency is also related to the increased negative intrapulmonary pressure, since blood is hampered in its exit from the lungs to the left ventricle and from the left ventricle into the extrathoracic aorta. Palpation of the pulse in patients with severe asthma will frequently reveal a diminution in volume at the end of inspiration and an increase in volume during expiration when the pressure within the chest falls toward atmospheric pressure. Attempts then to lower the abnormally elevated negative pressure within the lungs by inhalational therapy include oxygen, which lowers the volume of breathing, and helium-oxygen mixtures and pressure breathing, each of which decreases the physical effort of respiration and provides more efficient alveolar ventilation.

Continuous nebulization of 1:100 epinephrine and 1 per cent neosynephrin, frequently 0.5 cc. of each mixed in a single dose, may be used three to five times in twenty-four hours, since local bronchovasconstriction and bronchodilation may be produced. It has been frequently observed that patients cough after inhalation of the nebulin of these drugs and expectoration of mucus and mucopurulent secretion is aided. This is generally carried out by a flow of 5 liters of oxygen per minute through a fine nebulizer; the use of helium-oxygen mixtures for this purpose has the additional

advantage of penetrating alveoli that may be impervious to oxygen.

Intravenous administration of aminophyllin, 0.48 Gm., is of conspicuous value in the majority of patients with status asthma. Intravenous administration of this drug should never be given within a period of less than eight minutes, since a number of patients have died as a result of sudden lowering of the venous pressure with inadequate return of blood to the right heart. The drug may also be injected intramuscularly or may be given rectally in somewhat larger dosage with a rubber catheter and 20 cc. glass syringe. For rectal administration the dose may vary from 0.5 to 0.7 Gm. The advantage of this method is that effects on the circulation are very slight and that it may be used by a nurse, the patient's relatives or the patient himself. Aminophyllin administered once or twice in twenty-four hours for a period of four or five days may usher in a state of remission.

In patients with status asthma, refractoriness to adrenalin is almost always present. Unfortunately, in many cases aminophyllin refractoriness also develops. When this happens it is better to attempt to curtail the use of both adrenalin and aminophyllin as much as possible, reserving their administration to periods when the patient is in severe respiratory distress.

Bronchial relaxation under these circumstances is best obtained by the hypodermic or intramuscular injection of demerol in dosages of 50, 75, or 100 mg. every six, eight or twelve hours. Dizziness and nausea are less apt to take place with demerol if the first few doses of the drug are kept at 50 mg. until a tolerance has been obtained. Side-effects are also much less apt to occur if the patient lies quite still for a period of one hour after injection. In over 200 patients treated with demerol there was no evidence of physical addiction. Two patients had to be persuaded to stop the drug because of its mentally relaxing effect. The advantage of demerol over morphine is that respiratory depression has not been observed to take place following its use and no impairment of intestinal function occurs. In a few patients dilaudid in small doses, such as $\frac{1}{64}$ gr. may accomplish additional central nervous system and bronchial relaxation, but this drug must be given with awareness that larger dosages may produce respiratory depression. However, at times hypodermic injection of dilaudid in its full dose, gr. $\frac{1}{32}$, once or twice a day may terminate a state of intractable asthma. Under no circumstances should dilaudid be employed for a period of longer than five days, since addiction to this drug may readily take place.

Potassium iodide in saturated solution, 3 to 4 cc. daily, should be prescribed in all cases except those in which a known allergy or hypersensitivity to the drug is present. An increased secretion of mucus undoubtedly takes place in most cases, which helps in loosening bronchial plugs that are then more readily expectorated. The dosage may be reduced to 1 cc. twice a day after four or five days; in many cases this medication is continued for long periods.

Bronchoscopic suction is at times of life-saving value, especially in patients in whom the ciliary and peristaltic action of the bronchi have been so impaired as to result in inefficient and unproductive cough. The patient is rarely too ill to stand bronchoscopy, which is used not only for suction but also for the instillation of cocaine and adrenalin, and at times penicillin and streptomycin. In some cases in which suction is desired when the bronchoscopist is not available, the anesthetist on duty may insert a tracheal tube and suck out the mucus and plugs in the larger bronchi.

In cases that fail to respond to the measures that have been described above, ether anesthesia may be of very real value. This

attempt at deep bronchial relaxation is particularly suitable to those patients in whom severe bronchial spasm rather than excessive production of mucus is evident. Anesthesia may be given for forty minutes by inhalation or it may be administered rectally in dosages of 90 cc. of ether and 90 cc. of olive oil for the adult patient. After anesthesia it is important to turn the patient on his side, lower the head of the bed, and observe him so that one may not encounter the complication of the tongue falling backward and obstructing respiration. It is generally desirable to insert a nasal catheter, if the patient is not already being treated with oxygen, following ether anesthesia for a period of twelve to twenty-four hours to guard against anoxia as a result of depression of the respiratory center. The response of the patient to ether anesthesia is temporary during the period of its administration, the signs of bronchial spasm returning when the patient awakens. The beneficial results of ether are more apt to take place one or two days following anesthesia. In some cases a second anesthesia or even a third will promote a remission when the first treatment resulted in no improvement.

Fever therapy is not practical for those patients who are in a serious state of respiratory difficulty, but it is of marked value in many in whom intractable asthma persists in a border-line state of status asthmaticus. It may be produced by intravenous administration of 0.2 to 0.3 cc. of triple typhoid vaccine in a liter of saline or, in a more effective and easily controlled way, by the hyperthermia cabinet. In a few cases one course of fever of three to four hours of a temperature of 104° to 105°F. may produce a remission, but in most instances two or three exposures to fever therapy will achieve a more satisfactory state of symptom-free asthma. Although the remission does not generally last longer than three to six months, the symptoms of asthma, when they recur, are usually much less severe than prior to fever therapy.

Antibiotic therapy has been mentioned in the early part of our discussion. A number of observers have made reports, partly favorable and partly unfavorable, on the treatment of infectious asthma with penicillin, administered either intramuscularly or as an aerosol. At present, the effectiveness of this type of treatment cannot be appraised since more experience both in the method and in the interpretation of results is required. A relatively small percentage of patients with intractable asthma have been greatly benefited by penicillin treatment, especially those in whom penicillin-sensitive organisms are present as the predominating organisms in the sputum culture. The use of penicillin aerosol is of special value in the treatment of sinusitis that may be associated with infectious asthma when it is administered by means of intermittent production of negative pressure in the nasal accessory passages and sinuses.

When the state of intractable asthma has been overcome by adequate therapy and by time itself, subsequent treatment must naturally be highly individualized. The most common error in management of status asthmaticus at this time is allowing the patient to resume increasing activity too soon. In most cases convalescence is allowed to take place far more quickly than that which follows pneumonia, although the experience of status asthmaticus is often far more shocking to the patient.

Sedatives, especially phenobarbital, and demerol by mouth may be useful in aiding the patient to remain in a relaxed state for a considerable period following severe asthma A very gradual return to full activity should be recommended.

A Doctor: What is the present status of the use of potassium iodide in asthma?

Dr. Barach: Administration of potassium iodide maintains a freer flow of mucus

and prevents crusting, in that way increasing the ease of expectoration. Excessive use may result in bronchorrhea.

DR. LOEB: I wonder if experiments have been done to measure bronchial secretion before and after administration of iodides in animals with bronchial fistula?

DR. BARACH: I do not know of such experiments.

DR. SANDERS: Would Dr. Barach say more about the intermittent use of helium-oxygen mixtures to break tolerance to epinephrine and aminophyllin?

DR. BARACH: In about 60 per cent of a large series of patients with intractable asthma intermittent use of helium-oxygen mixtures for four or five days restored responsiveness to both epinephrine and aminophyllin.

DR. I. MUFSON: What has been the experience with the use of benadryl and pyribenzamine in asthma?

DR. LOEB: Reports indicate that approximately 60 per cent of asthmatic patients experience some amelioration with benadryl.

DR. BARACH: About 15 per cent of my cases of asthma have shown significant improvement with benadryl, which is much more useful in hay fever. I have had no experience with pyribenzamine but understand that it is similar to benadryl in effectiveness though perhaps less valuable.

STUDENT: Are asthmatic attacks sometimes precipitated by penicillin or sulfonamides?

DR. LOEB: Yes. These agents should be used cautiously in patients with a history of bronchial asthma, particularly if administered by inhalation.

DR. BARACH: Penicillin may provoke acute asthmatic seizures, particularly if the patient becomes allergic to it as manifested by urticaria. Urticaria following penicillin occurs much more frequently in asthmatic than in non-allergic patients. When administered by aerosol, penicillin should be given as the calcium salt or the *crystalline* sodium salt, the latter being much less apt to provoke coughing or to cause sensitivity, as evidenced by urticaria.

STUDENT: Should any special precautions be taken with penicillin?

DR. BARACH: No. Since benadryl is almost specific for the control of urticaria, this complication is no longer a serious one.

DR. ATCHLEY: It might be wise to close the clinic with re-emphasis of the reasons why morphine should not be used in bronchial asthma. It is a respiratory depressant to which asthmatics are particularly vulnerable; and its use in the management of bronchial asthma has resulted all too often in addiction.

DR. LOEB: There is no question today but what demerol should be employed in preference to morphine. There are three reasons for this: (1) Because demerol relaxes bronchial spasm. (2) It is less apt to result in habituation or addiction. (3) It has less depressant effect on the respiratory center than morphine.

Summary. The basic abnormality in bronchial asthma is contraction of the bronchial, and particularly of the bronchiolar smooth muscle, producing narrowing and varying degrees of obstruction of the air-conducting passages. Other factors dependent upon this original defect may aggravate the condition. Thus, when the muscular wall of the bronchiole contracts the mucous membrane may be thrown into folds, causing further narrowing of the lumen. Increased mucous secretion, exudate due to infection, or edema resulting from greatly increased intrapulmonary negative pressure may be critical factors in accentuating the severity of obstruction.

Breathing obviously is difficult and, because more force is required, the accessory muscles of respiration come into use. With this added work, air may be sucked in but is not expired if the elastic recoil of the lungs

fails to overcome the obstruction. Eventually, if the process continues, the lungs fill with air and the chest is held in the position of maximum inspiration, one which tends ordinarily to widen the bronchial lumen.

At this point, respiration is shallow and slower than normal. The vital capacity is reduced because the lungs cannot be fully deflated. The residual air increases for the same reason; as a corollary, the residual air: total air capacity ratio increases and this is accompanied by a fall in total air capacity when the alveoli are obstructed. Intrapulmonary mixing is reduced since free flow of air within the lung is either slowed or arrested. Alveolar O_2 falls because it is not replenished as fast as it is absorbed by the blood, and alveolar CO_2 rises since it cannot be exhaled. The blood O_2 saturation tends to fall while the blood CO_2 content tends to rise. Cyanosis and dyspnea are present. In the most severe states death from anoxia may ensue.

These are the dramatic and serious findings in severe asthma. It is of importance that the asthmatic subject in the asthma-free state shows evidence of a continuing disturbance in pulmonary physiology. A reduction in maximum breathing capacity characterized by diminution in both the volume and rate of respiration, together with faulty intrapulmonary mixing, may be present. That a considerable degree of increased bronchiolar muscle constriction is responsible is suggested by the response to bronchodilator drugs.

Our knowledge relative to the causative mechanism in asthma is in some respects more theoretical than practical. Specific antigen-antibody reactions characterize experimental allergy. In these states, sensitivity, which may be passively transferred, is proportional to the serum antibody (precipitin) titer.

In human allergic asthma, on the other hand, titratable antibody cannot be demonstrated, although specific sensitivity may be passively transferred. This is apparently due to a naturally occurring thermolabile sensitizing substance called reagin, which occurs in amounts too small to be measured by serological technics. When an allergic patient is desensitized by injection with a specific allergen, a heat-stable antibody is formed which inhibits the allergic response the allergen would otherwise initiate. Clinical improvement appears to be correlated with the concentration of this antibody.

Every attempt should be made to determine what allergens are causative and a no less assiduous effort made to remove them from the patient's environment. This applies to the so-called exogenous varieties as well as to the endogenous bacterial allergens. Frequently, however, non-specific irritants are responsible secondarily for asthmatic attacks. The fact that asthmatics show abnormal pulmonary function even when asthma-free helps to explain the rôle of non-specific irritants, exercise and emotional disturbances in precipitating an asthmatic attack; it also emphasizes the necessity for evaluating and controlling these factors to obtain maximum benefit.

The patient with bronchial asthma often presents a far more complex problem than that of his specific allergic response. Management frequently requires an analysis of the individual as a whole and his relation to his environment. The internist should qualify himself to make such an analysis, in most instances assuming the major responsibility for treatment. The cooperation of the patient should be enlisted by explanation and instruction in order to work out the most efficient regimen for management of his individual problem. The most important step, of course, is to seek specific antigens and attempt to remove them from the environment. Careful history taking with informed cooperation of the patient, and the method of trial and error by experi-

mental control of the environment form the basis for investigation. Skin-testing technics are of limited reliability.

Respiratory infection is an important factor in many cases, requiring careful examination of the whole respiratory tract and elimination of infection if possible. The rôle of possible pulmonary irritants should be investigated. Emotional trauma is a precipitating factor in so many instances that the emotional problems of the patient should never be neglected.

The acute asthmatic attack responds best to epinephrine given by repeated subcutaneous injection. Intravenous or rectal aminophyllin is also highly effective. The anti-histaminic drugs, though not yet extensively tried, give promise of definite value.

The treatment of status asthmaticus especially requires persistence, patience and nicety of judgment. Oxygen and helium-oxygen mixtures tend to decrease anoxia, ease breathing and allow the distended alveoli to empty during expiration. Under pressure, the same gases may be effective in reducing congestion, preventing or suppressing pulmonary edema, and increasing the patency of the bronchi. To promote bronchial relaxation, epinephrine parenterally or by nebulization and aminophyllin by rectum or vein should be given in the dosage necessary for individual requirements, but often the patient in status asthmaticus has become refractory to these drugs. In this situation, demerol may prove of great value as a bronchial relaxant. Extreme measures include ether anesthesia, bronchoscopy and fever therapy.

Case Report

Suppurative Complications of Bland Pulmonary Infarcts Accompanying Congestive Heart Failure*

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PLEURAL effusions complicating pulmonary infarctions are generally well recognized. Gsell noted such effusions in one-half of his cases of pulmonary infarction.[1] In fact, obstinate, seemingly primary pleural effusions in patients with heart disease should always suggest pulmonary infarction.[2] These effusions are serous, serofibrinous or serosanguineous, and the origin of the fluid is thought to be a transudation. Intrathoracic suppuration rarely follows pulmonary infarcts, but perhaps frequently enough for the clinician to be aware of its existence. Moreover, most text books on heart disease fail to mention suppurative necrosis or the suppurative pleuritis which may occur concomitantly. White, in his book fails to mention this complication of pulmonary infarction, although he stresses pulmonary infarction itself as a frequent complication of congestive failure.[3] Friedman, in reporting 276 cases of lung abscess from the Boston City Hospital, from the standpoint of etiology, fails to mention secondary infection of a bland hemorrhagic infarct as a cause.[4] Steinberg, Clark and De La Chapelle, however, have reported five cases, one patient being successfully treated by surgical intervention; they emphasized the original bland nature of the infarct and pointed out that secondary infection took place by the bronchial route from organisms present in the respiratory passages.[5] Chester and Krause more recently have reported seventeen such cases, of which only six were diagnosed antemortem.[6] The source of these infarcts may be either the right auricular appendage, right auricle, right ventricle or the peripheral venous system. Spontaneous thrombosis in a pulmonary artery may also give rise to lung infarcts.

It is not within the scope of this paper to discuss the relative importance of autochthonous thrombosis or the embolic origin of pulmonary infarction. This has been ably done by Belt.[7,8] Regardless of the origin of the pulmonary arterial occlusion and the ensuing infarction, secondary infection may occur by the bronchogenic route from organisms present in the tracheobronchial tree. Van Allen, Adams, and Hrdina, showed the ease of production of chronic lung abscesses in dogs by intrabronchial contamination of pre-existing bland infarcts produced by aseptic emboli.[9] Rosenblatt[10] and Neuhoff and Touroff[11] have emphasized gross infection of teeth and gums and the aspiration of septic tartar into the lungs in the pathogenesis of chronic lung abscess. Certainly, hemorrhagically infarcted pulmonary tissue is a good nidus for secondary

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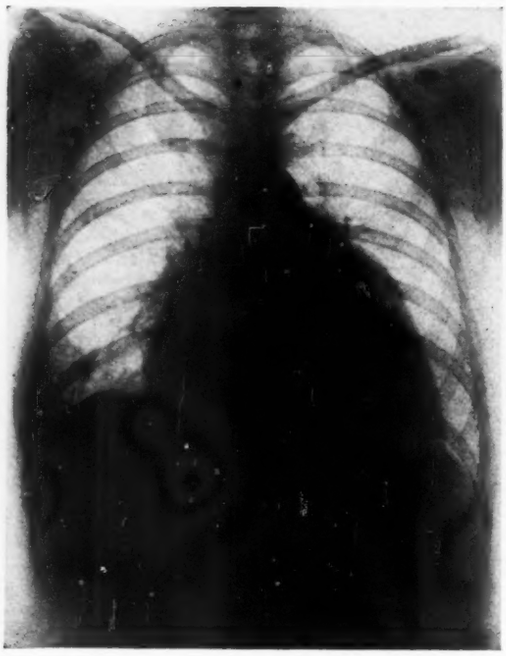

FIG. 1. *Roentgenogram made on admission, showing typical mitral configuration of cardiac silhouette.*

contamination and it is surprizing indeed, that these do not become necrotic more often. Schwedel[12] points out that suppuration of bland pulmonary infarcts may occur and that empyema may accompany them.

Because of the lack of emphasis placed on this condition by the various available medical texts and the medical literature in general, we believe that a report of the following case is of more than academic interest:

CASE REPORT

M. G., a forty-three year old white female, was admitted to the medical service of the Newark Beth Israel Hospital on November 30, 1945, complaining of increasing dyspnea, orthopnea, palpitations and swelling of the feet and ankles. The patient stated that she had had rheumatic polyarthritis at the age of eight, with involvement of multiple symmetrical joints which were red, hot and swollen; she was confined to bed for several months. The rest of her past history was non-contributory. She had been in good health until one year prior to her admission, when she noted the insidious onset of her symptoms. Her physician prescribed digitalis and the patient improved for about seven months, when she became nauseated and discontinued the drug without her doctor's consent. Several days prior to admission the symptoms of diminished cardiac reserve appeared again and the patient was referred to the Hospital.

Physical examination revealed an adult female in acute distress, dyspneic, orthopneic and cyanotic. Examination of the external ocular muscles was normal; the fundi were normal; conjunctivae showed no petechiae, pallor or inflammatory changes. The neck showed distended cervical veins. No lymphadenopathy or thyroid enlargement were noted. The point of maximum intensity of the heart beat was in the fifth interspace outside the midclavicular line. A loud, high-pitched systolic murmur was heard over the entire precordium; the second pulmonic sound was accentuated more than the second aortic and the rhythm totally irregular with a ventricular rate of 124 per minute, and a pulse rate of 108. Blood pressure levels were obtained at 170 systolic, 110 diastolic. Examination of the chest revealed dullness over both lower lobes posteriorly with diminished breath sounds and many medium moist râles. The liver was palpable 8 cm. below the costal margin and exquisitely tender. The extremities showed marked pitting pretibial edema. There were no petechiae or clubbing, and the finger nail beds were extremely cyanotic. Neurologic examination was essentially negative. The admitting diagnosis was rheumatic heart disease, chronic, inactive; enlarged heart; mitral stenosis; mitral insufficiency; auricular fibrillation. (Class 4E)—Essential hypertension.

The urine showed a specific gravity of 1.021 with protein 78 mg.; microscopic examination showed 2 to 21 red blood cells per high power field. In the hematologic examination the white blood cells varied from 8,800 to 22,200 with 70 to 87 per cent polymorphonuclears, with a shift to the left. The red blood cell count was 4,600,000 with a hemoglobin of 88 per cent; blood urea nitrogen—22 mg. per cent and blood sugar—115 mg. per cent; serum proteins—4.4 gm. per cent; serology revealed nothing abnormal.

The patient was digitalized immediately and the cough, which was a very disturbing feature on admission, began to subside, the lung fields

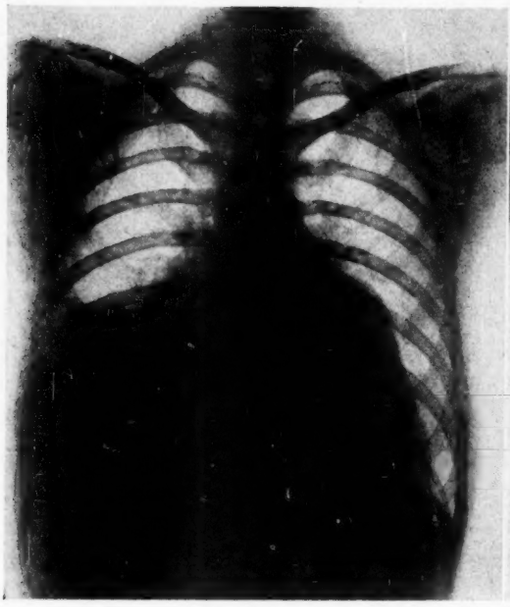

FIG. 2. *Roentgenogram made after clinical manifestations of pulmonary infarction. Note convex density of the right lower lung field the upper margin of which presents the typical Ellis Line of a hydrothorax. Fluid at this time was serosanguineous and sterile on culture.*

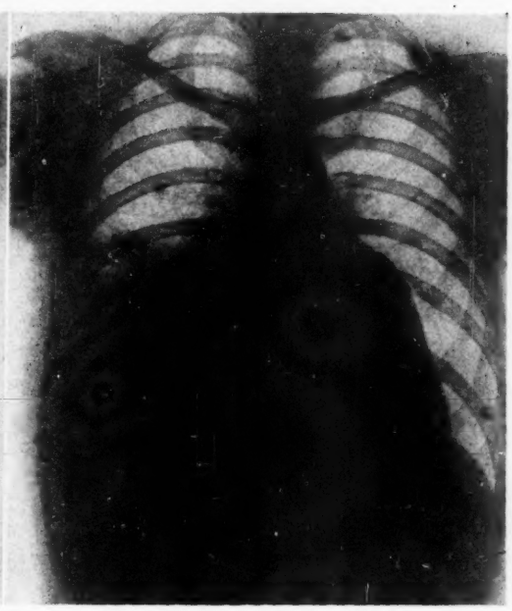

FIG. 3. *Roentgenogram made after patient developed foul expectoration. An increase in fluid may be seen and a definite fluid level may be noted in the third anterior interspace, indicating a pyopneumothorax and suggesting a putrid empyema.*

appearing much clearer on auscultation. In fact, *x*-ray examination on December 3, 1945, was reported: "mitral valvular disease with lung fields of good aeration." On December 5, 1945, the patient complained of feeling uncomfortable and the temperature rose abruptly. A pulmonary infarct was suspected in spite of negative physical findings. The temperature persisted, fluctuating between 99.4°F. and 102.0°F. On December 10, 1945, a diagnosis of fluid in the right chest was made clinically and confirmed by *x*-ray examination. At this time the patient complained of an increased cough with severe pain in the right chest, often referred to the right shoulder and aggravated on breathing. From this time on, the course was progressively down hill. The cough became a very disturbing factor and on January 5, 1946, the patient began to expectorate copious quantities of foul-smelling sputum; her breath also was very offensive. *X*-ray examination now showed a marked increase in fluid and at the level of the fourth anterior rib a definite fluid level could be seen. The diagnosis of a putrid empyema, secondary to a ruptured putrid lung abscess, was made and fluid was aspirated. This yielded 100 cc. of a thin, opalescent fluid with a foul odor; 50,000 units of penicillin were instilled intrapleurally at this time, and intramuscular injection of 30,000 units every three hours was begun. Culture of the aspirated fluid showed pneumococci and Streptococcus viridans. Unfortunately, no anaerobic cultures were made. A surgical consultation was ordered and the patient was seen by Dr. Henry Brodkin of the Thoracic Surgery Department, who agreed with the diagnosis and advised immediate thoracotomy. His operative findings were as follows: "A large right putrid empyema space was found, surrounded by the right diaphragm and the collapsed right lower lobe along its lateral and posterior surfaces. The space was filled with foul air and thick, foul pus. The right paravertebral segment of the right lower lobe contained an area of broken down pulmonary tissue, which was the seat of a necrotic infarct. No broncho-pleural fistula was noted at this time." Cultures of the material were the same as those taken from the fluid removed at aspiration.

For a while, the patient seemed to improve following the operation. Her temperature subsided, cough diminished and she felt consider-

ably better. However, on January 12, 1946, the patient suddenly became very stuporous; there were no localizing neurological signs. Cerebral embolization was suspected. From this point her course again became stormy; the temperature rose, but her sensorium improved. Blood cultures at this time were negative. On January 31, 1946, the vision in her left eye became impaired. An eye consultation by Dr. A. Rados, revealed "several discrete vitreous opacities; the disc appeared veiled; veins were markedly dilated and tortuous; in the extreme nasal periphery a large grey exudative patch could be seen. Diagnosis: Metastatic choroiditis." By now, the spleen, which had never been palpable, could be felt about three fingers' breadth below the costal margin. No change in the character of the murmurs was noted. Blood cultures on two occasions were positive for Staphylococcus albus. Whether these were contaminants or truly significant is a matter of conjecture. The patient died suddenly on February 7, 1946, after a stormy course characterized by high temperature and progressive heart failure. No autopsy could be obtained.

The various clinical features of pulmonary infarctions have been thoroughly discussed by many authors. Suffice it to say that the clinical manifestations may be very mild, indeed; for example, a rise in temperature, an increase in respiratory rate or pleuritic pain, may be the only presenting symptoms. Our patient is a good case in point, having shown only an increase in temperature and pleuritic pain as the presenting symptoms of infarction. Blood-spitting, which is so often thought to be an invariable sign, did not occur here. Kensey and White, in their discussion of fever in congestive heart failure, noted that it was usually the result of some complication and very often this complication was pulmonary infarction.[13] Suppuration in bland pulmonary infarcts, on the other hand, is only rarely seen; its origin is probably due to bronchial contamination. As previously mentioned, Steinberg, Clark and De La Chapelle showed by careful microscopy the presence of suppurative necrosis in the areas of hemorrhagic infarction, with areas of amorphous débris, surrounded by dense zones of polymorphonuclear infiltration.[5] In none of the five reported cases was the necrosis putrid, and only in one instance did the suppuration complicate a recent infarction. Only in this case did the initial tap yield frank pus. In the other cases suppuration occurred in older infarcts and several aspirations yielded serous or serosanguineous fluid, sterile on culture. In such instances, the introduction of organisms from without through needle puncture must be ruled out. However, the finding of necrotic areas in the pulmonary infarct at postmortem examination proved infection of the pleural fluid from the parenchymal lesion and not from external contamination. Thus, we may readily assume that although the infarct may be present for some time and the pleural fluid may remain uninfected for a variable period, even extending to several months, infection ultimately may occur. This is confirmed by the experience of Chester and Krause, who also found infarction preceding the clinical evidence of pulmonary suppuration by a varying interval.[6] Our case is similar to those reported by these authors in that the suppuration was putrid and probably due to anaerobic organisms, and that actual rupture of the infected infarct took place into the pleural cavity, giving rise to a putrid empyema. The organisms responsible for this lesion most likely came from infected gingival secretions, the conditions necessary for their propagation having arisen from bronchial occlusion secondary to the bronchospasm, exudation and edema accompanying the pulmonary infarction.

The importance of correctly diagnosing suppurative complications of pulmonary infarctions is self-evident. Touroff[14] and Eggers[15] have reported recovery following

surgical drainage. These patients, of course, are not good surgical risks, but at least surgical drainage will offer some a chance for survival. In our case, recovery from operation was apparently hampered by the development of sepsis, as evidenced by the metastatic suppurative choroiditis and the splenic enlargement. Such sepsis may have been due to an acute bacterial endocarditis, superimposed on the chronic rheumatic valvulitis, or perhaps a septic thrombophlebitis of a pulmonary vein in the area of suppurative necrosis. The operative site, according to the surgeon, had been cleared of infection, but certainly this fact does not entirely militate against such a diagnosis.

SUMMARY

1. A case of putrid intrathoracic suppuration following bland pulmonary infarction is reported.

2. The bronchial route of contamination of the bland infarct is stressed.

3. The importance of early recognition of pulmonary suppuration following infarction is emphasized, inasmuch as surgery holds out the only hope of cure.

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Editorial

Folic Acid

In a recent joint announcement, two groups of investigators[1] made public the results of their successful investigation of the structural formula of liver *Lactobacillus casei* factor, together with methods of synthesis of crystalline, biologically active material. The formula established for liver *L. casei* factor was N-[4-{[(2-amino-4-hydroxy-6-pteridyl) methyl] amino} benzoyl] glutamic acid. As a convenient and appropriate abbreviation for this compound the designation pteroylglutamic acid was proposed.

The authors also clarified the relationship of liver *L. casei* factor to fermentation *L. casei* factor and to *Streptococcus faecalis* R factor, all of which have been included at times under the general term "folic acid." It was shown that anaerobic alkaline hydrolysis converted fermentation *L. casei* factor into liver *L. casei* factor with the liberation of two moles of an alpha-amino acid, subsequently identified. A compound which was active for *Str. faecalis* R (but not for *L. casei* or normal growth and hemoglobin formation in the chick) was obtained by substituting *p*-aminobenzoic acid for the *p*-aminobenzoylglutamic acid used in the synthesis of *L. casei* factor.

The chemical identification and synthesis of these compounds marks an important step forward in the study of a new class of substances of exceptional interest. It is already clear that synthetic liver *L. casei* factor is an effective agent in the treatment of macrocytic anemias characterized by megaloblastic arrest. Its efficacy as an antisprue factor has been well established by the work of Spies[2,3] and of Darby[4] and their associates. Within a few days of institution of therapy there is a marked subjective change characterized by alertness, vigor, improved appetite and sense of well being. Relief of glossitis and regeneration of lingual papillae soon follow, along with cessation of diarrhea which occurs without any significant change in the fat content of the stools. There is a considerable weight gain beginning on the fifth to seventh day, at first largely due to retention of water. The hemopoietic response is initiated by an increase in reticulocytes on the third to sixth day of treatment, the peak rise usually occurring on the sixth to eighth day and reaching levels similar to those obtained with liver extract. The red blood cell count increases correspondingly, together with a marked rise in platelets and some increase in white blood cells. Bone marrow studies show decrease of megaloblasts with normoblastic predominance. It is of interest that the response in "non-tropical" sprue is the same as in "tropical" sprue, further evidence that there is no essential difference between these disorders and that both are deficiency states caused by inadequate gastrointestinal absorption of folic acid and probably of other factors.

[1] Angier, Robert B., Boothe, James H., Hutchings, Brian L., Mowat, John H., Semb, Joseph, Stokstad, E. L. R., Subbarow, Y. and Waller, Coy W. Cosulich, Donna B., Farhrenbach, M. J., Hultquist, M. E., Kuh, Erwin, Northey, E. H., Seeger, Doris R., Sickles, J. P. and Smith, James M., Jr. The structure and synthesis of the liver *L. casei* factor. *Science*, 103: 667, 1946.

[2] Spies, Tom D., Vilter, Carl F., Koch, Mary B. and Caldwell, Margaret H. Observations of the antianemic properties of synthetic folic acid. *South. M. J.*, 38: 707, 1945.

[3] Spies, Tom D. Effect of folic acid on persons with macrocytic anemia in relapse. *J. A. M. A.*, 130: 474, 1946.

[4] Darby, William J., Jones, Edgar and Johnson, Howard C. Effect of synthetic Lactobacillus casei factor in treatment of sprue. *J. A. M. A.*, 130: 780, 1946.

Striking responses to synthetic folic acid are obtained also in nutritional macrocytic anemia, addisonian pernicious anemia, pernicious anemia of pregnancy and megaloblastic anemia of infancy. This last disorder, recently described by Zuelzer and Ogden,[5,6] appears to be common in white infants under the age of eighteen months. It is characterized by severe normochromic anemia, usually but not always macrocytic; by a tendency to leukopenia and neutropenia, a decrease in platelets and a megaloblastic bone marrow pattern or one intermediate between the megaloblastic and normoblastic types. The response to treatment with folic acid is so striking as to indicate that megaloblastic anemia of infants, like sprue and nutritional macrocytic anemia in adults, is essentially a folic acid deficiency syndrome.

Aplastic anemias, iron deficiency anemia, anemia accompanying leukemia, anemia of prematurity and certain other forms of anemia have proven refractory to folic acid therapy. Satisfactory hemopoietic responses are obtained, apparently, only in macrocytic anemias accompanied by hyperplastic marrow.

The evidence indicates that pteroylglutamic acid is an important maturation factor, performing some specific function in the maturation of erythrocytes and probably also of other formed elements of the blood. This property, together with the remission produced in addisonian pernicious anemia, has aroused much speculation as to the relation between folic acid and the antianemia principle of liver; particularly between the chemical structure of folic acid, now clarified, and that of liver antianemia principle, as yet unknown.

That the two substances are not identical as to therapeutic effects is evident. The amount of purified liver antianemia principle which will produce remission in addisonian pernicious anemia is much less than the requisite dosage of pure synthetic folic acid which, moreover, has proven disappointing thus far in the treatment of combined system disease; consequently synthetic folic acid therapy does not appear to be indicated in addisonian pernicious anemia except in subjects sensitive to liver extract. On the other hand, the efficacy of crude liver extracts in sprue and nutritional macrocytic anemia probably derives in large part from their folic acid content. Liver therapy in these disorders is being displaced by synthetic folic acid orally administered.

There is one point of similarity in the chemical composition of the two substances: folic acid is a glutamic acid derivative and liver antianemia principle contains a relatively high proportion of this amino acid. The significance, if any, of this circumstance is not clear nor is any other chemical relationship between the two substances apparent at this time. Nevertheless, the striking success achieved in elucidating the structure of folic acid would suggest that the time may be ripe for a concerted attack upon the obscurities of the constitution of the antianemia principle of liver.

A. B. G.

[5] Zuelzer, Wolf W. and Ogden, Faith N. Megaloblastic anemia in infancy: a common syndrome responding specifically to folic acid therapy. *Am. J. Dis. Child.*, 71: 211, 1946.

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Book Review

THE Norton Medical Award is given annually to encourage the writing of books on medical topics for the layman. Last year's winner, "The Doctor's Job," by Carl Binger, was a particularly able effort which did much to further the patient's understanding of the complexities of modern practice.

This year, a very different subject has been selected. "Doctors East, Doctors West"* relates the experiences, impressions and accomplishments of an American physician in China during the first quarter of the present century. Apparently destined to follow in the footsteps of his father and grandfather, Dr. Hume had begun work in India when the call to China came. Hunan province had just been opened to foreigners in 1905 and the people were suspicious. In the capital city of Changsha Dr. Hume selected an unused inn and so began the medical division of the tremendously successful Hunan-Yale educational project. How he won the confidence of the population and built his dispensary into a modern medical center comprising a four hundred bed hospital, nursing and medical schools is well and modestly told.

But perhaps of more interest to the average reader will be the picture of the Chinese people presented. The author knows the rank and file as well as the upper strata of Chinese society and has witnessed its evolution from the days of the dynasty to the era of Chiang Kai-Shek. One is left with the impression that the average Chinese, like the average American, is a fairly stable citizen, a heartening conclusion perhaps in these unsettled times.

The book is pleasantly written and contains several photographs. It would provide an interesting and instructive evening for anyone concerned with medical missionary work in China.

F. K. H.

* DOCTORS EAST, DOCTORS WEST. By Edward H. Hume, M.D. Cloth. Pp. 278, with frontispiece and 21 illustrations. New York, 1946. W. W. Norton and Company. *Price* $3.00.

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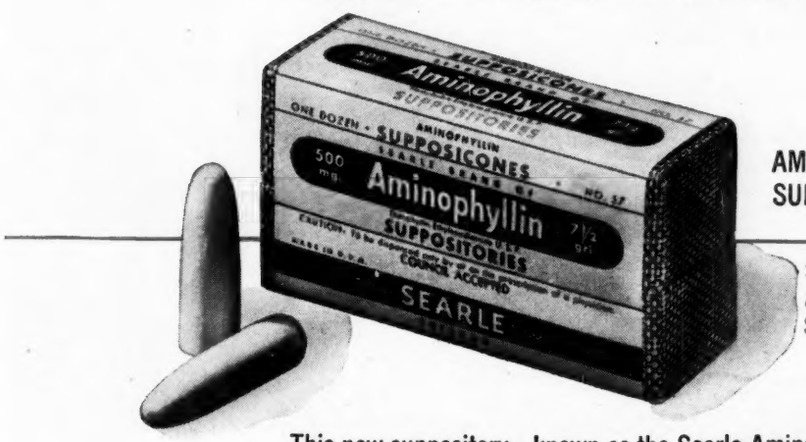

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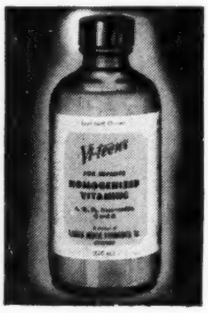

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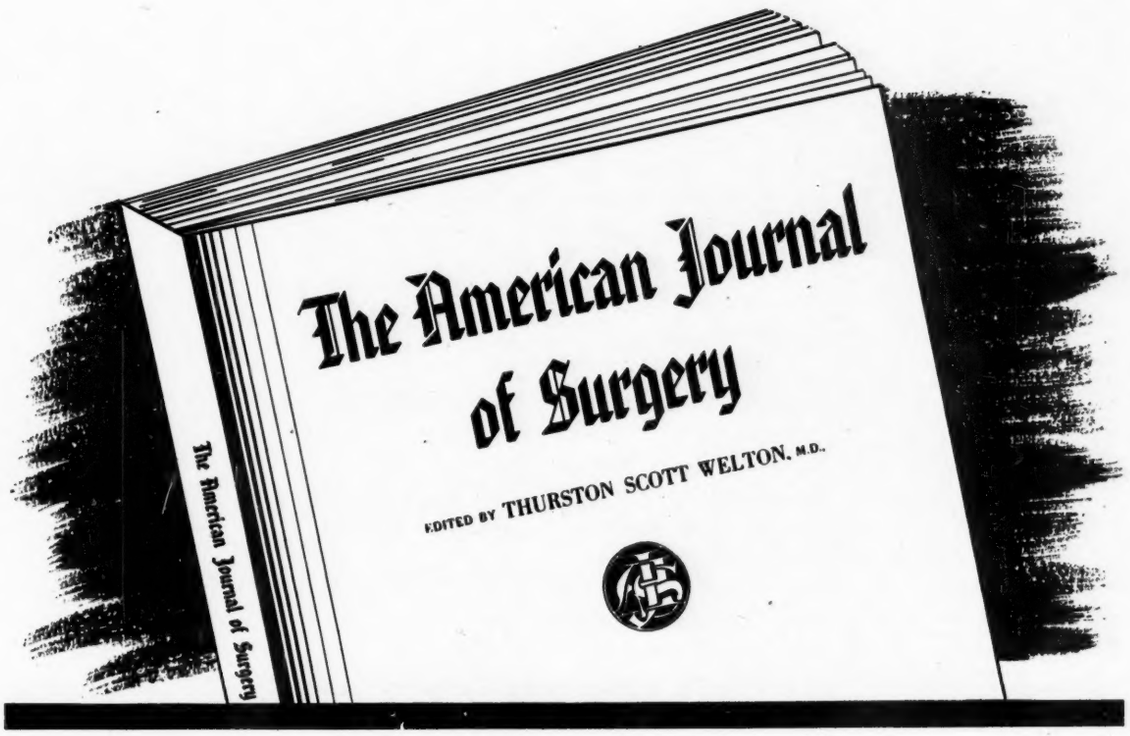

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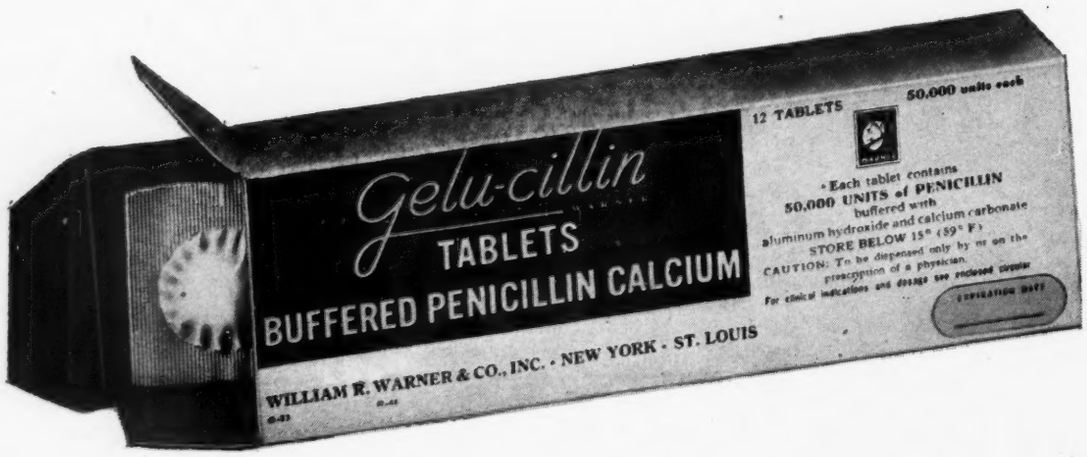

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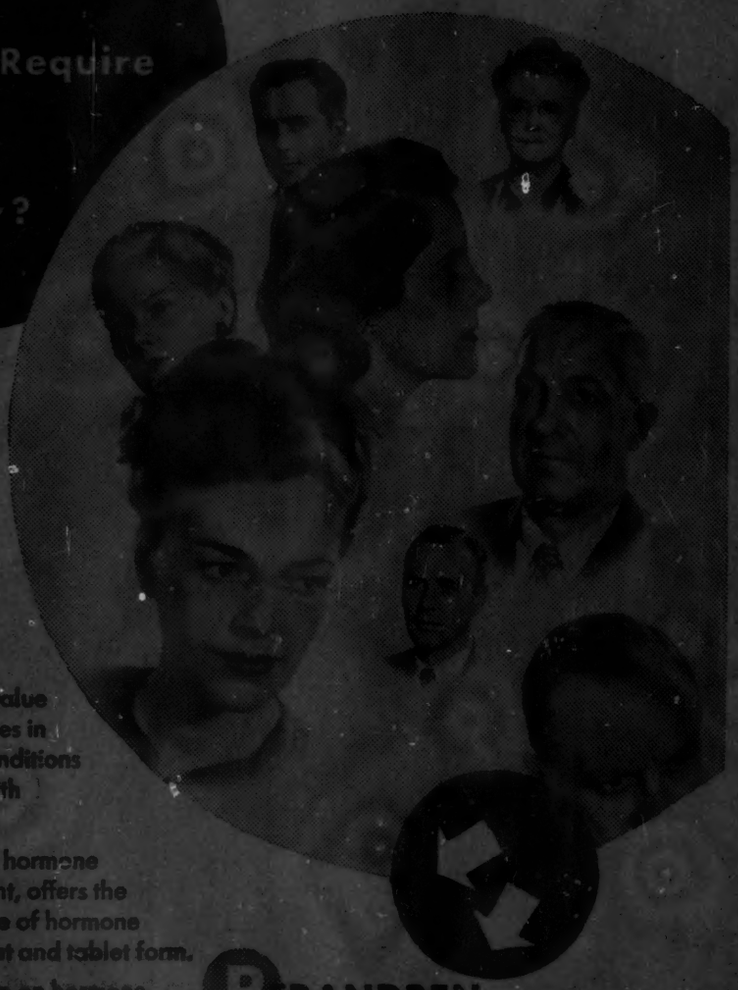

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